A CASE

OF

MULTIPLE MYELOMA (MYELOMATOSIS) WITH BENCE-JONES PROTEID IN THE URINE

(MYELOPATHIC ALBUMOSURIA OF BRADSHAW, KAHLER'S DISEASE)

AND A

SUMMARY OF PUBLISHED CASES OF BENCE-JONES ALBUMOSURIA

BY

F. PARKES WEBER, M.D., F.R.C.P.

PHYSICIAN TO THE GERMAN HOSPITAL

WITH A REPORT ON THE CHEMICAL PATHOLOGY

BY

DR. R. HUTCHISON AND DR. J. J. R. MACLEOD

[*From Volume 86 of the 'Medico-Chirurgical Transactions'*]

LONDON

PUBLISHED BY THE ROYAL MEDICAL AND CHIRURGICAL SOCIETY, AND SOLD BY H. K. LEWIS, 136, GOWER STREET, W.C.

1903

ADLARD AND SON, PRINTERS] [LONDON AND DORKING.

PRICE TWO SHILLINGS Net.

A CASE

OF

MULTIPLE MYELOMA (MYELOMATOSIS) WITH BENCE-JONES PROTEID IN THE URINE

(MYELOPATHIC ALBUMOSURIA OF BRADSHAW, KAHLER'S DISEASE)

AND A

SUMMARY OF PUBLISHED CASES OF BENCE-JONES ALBUMOSURIA

BY

F. PARKES WEBER, M.D., F.R.C.P.

PHYSICIAN TO THE GERMAN HOSPITAL

WITH A REPORT ON THE CHEMICAL PATHOLOGY

BY

DR. R. HUTCHISON AND DR. J. J. R. MACLEOD

[*From Volume 86 of the 'Medico-Chirurgical Transactions'*]

LONDON

PUBLISHED BY THE ROYAL MEDICAL AND CHIRURGICAL SOCIETY, AND SOLD BY H. K. LEWIS, 136, GOWER STREET, W.C.

1903

A CASE

OF

MULTIPLE MYELOMA (MYELOMATOSIS) WITH BENCE-JONES PROTEID IN THE URINE

(MYELOPATHIC ALBUMOSURIA OF BRADSHAW, KAHLER'S DISEASE)

AND A SUMMARY OF PUBLISHED CASES OF BENCE-JONES ALBUMOSURIA

BY

F. PARKES WEBER, M.D., F.R.C.P.

PHYSICIAN TO THE GERMAN HOSPITAL

WITH A REPORT ON THE CHEMICAL PATHOLOGY

BY

DR. R. HUTCHISON AND DR. J. J. R. MACLEOD

Received October 23rd, 1902—Read March 10th, 1903

THE patient, J. T—, aged 50, a stoker, came under my observation at the German Hospital in May, 1900, but I did not make the diagnosis of multiple myeloma until the following July, when I happened to examine the urine by the ordinary methods. From May to July the Bence-

Jones proteid[1] in the patient's urine had been frequently, at one time daily, measured by Esbach's albuminimeter, but had been entered in the notes as ordinary albumen. The daily amount of urine was found to be about 2000 c.c., and it contained about 7 per mille of the proteid. The reactions, as afterwards ascertained, were quite typical, just as those described by Bradshaw, Kühne, Bence-Jones, and others. The most characteristic are, I think, the following (that is, when the urine is acid[2]) :—Coagulation of the proteid at a much lower temperature (about 58° C.) than ordinary albumen, more or less solution of the precipitate at a higher temperature (*e. g.* when the urine is boiled), and complete or almost complete solution on adding acetic acid to the boiling urine ; after the precipitate has been partially re-dissolved by boiling, a characteristic re-precipitation should take place on allowing the urine to cool. What Dr. Bradshaw considered to be the spontaneous precipitation of the proteid in his case (noted also in some other cases) was likewise observed in the urine of the present case. The urine sometimes was turbid with this precipitate when quite freshly passed, and on these occasions, the reaction being always very acid, the turbidity could not be due to phosphates. Exact details in regard to the urine are contained in the following history of the case, which includes reports on the urine by Dr. R. Hutchison.

[1] On account of the contention by A. Magnus-Levy (Hoppe-Seyler's 'Zeit. f. phys. Chemie,' Strassburg, 1900, vol. xxx, p. 200) that the so-called Bence-Jones albumose is really an albumen, I have referred to it in this paper as Bence-Jones proteid. For the sake of brevity, however, I have sometimes spoken of "Bence-Jones albumosuria," when I meant to signify the presence of Bence-Jones proteid in the urine. It seems that precipitin experiments fail to solve this question of the nature of the Bence-Jones proteid. In fact, the so-called "biological method" fails to distinguish the Bence-Jones proteid from various other proteids of human origin (*vide* Rostoski, "Zur Kenntniss der Präcipitine," 'Verhandl. der Phys.-med. Gesellschaft, Würzburg,' 1902, vol. xxxv, pp. 30—32).

[2] The urine is nearly always acid in Bence-Jones albumosuria cases.

Family history.—Father died at sixty-four. Mother died at ninety-three. A married sister, fifty-nine years of age, has diabetes. To be sure of this latter point I obtained a specimen of her urine on January 25th, 1901; it was of specific gravity 1042, clear, pale, of acid reaction, containing 6 per cent. sugar and a trace of albumen, and giving a reddish coloration on the addition of perchloride of iron (Gerhardt's reaction). Of the patient's five children, four are living and healthy, and the other is said to have died from an accident.

Patient's history.—He was always a strong man, and never remembers being seriously ill previously to present complaint. As a young man he had gonorrhœa and a sore on the penis (the latter at about the age of twenty-three), but he cannot recollect having had secondary syphilis. There is no history of alcoholism.

The patient thinks his present illness commenced about the end of 1899. On December 26th, 1899, he first noticed a tingling sensation in the finger-tips of the right hand, and could not hold a knife. He then seemed to improve, but towards the end of February, 1900, tingling and loss of power were gradually coming on in both hands, and at about the same time he began to suffer from pains in the loins. In the first part of May his back began to bend; attention was drawn to his stooping attitude. The loss of power in his hands necessarily compelled him to give up active work, but in spite of resting he felt exhausted.

Note on admission to the German Hospital (May 18th, 1900).—The patient is a stout, heavily built man (weight 84¼ kilogrammes), with a rather sallow complexion. His back is bent forward in walking, and his whole attitude and the way he holds his hands remind one somewhat of paralysis agitans. He complains of having very little power in his hands and fingers. His fingers are stiff and painful on movement, and are always slightly flexed at the metacarpo-phalangeal joints. He cannot voluntarily bend them so as to touch the ball of the thumb, and any attempt to bend them for him causes great pain. There

is a diffuse swelling of the backs of the hands, the puffy appearance of which is especially noticeable near the metacarpo-phalangeal joints. The hands are slightly tremulous, and are generally kept held up to his chest, as if that position were the most comfortable. The movements of the wrist and elbow-joints are free, but in regard to the shoulder-joints he experiences considerable difficulty in raising his arms so as to touch his head.

The area of cardiac dulness is slightly enlarged, and soft systolic murmurs are heard, attributable to the mitral and aortic valves. The lungs show nothing abnormal. There is a large, old, right inguinal hernia. Some pigmentation and scars on both shins are regarded by the patient as resulting from injuries at football. There is nothing special to note in regard to knee-jerks and cutaneous reflexes; there is no anæsthesia. The condition of the urine has already been alluded to, and more exact accounts will be given later on.

Under treatment, chiefly by rest, local hot baths, electricity, and slight massage, the condition of the hands seemed to improve somewhat, so that, when patient left the hospital on July 5th, 1900, he could bend his fingers sufficiently to touch the ball of the thumb.

The patient, after leaving the hospital, was seen from time to time. On July 16th, 1900, when he came up for examination, the kyphosis in the dorsal region was *very* noticeable. He had some difficulty in getting up from the sitting position, but could walk without the help of a stick. The pulse was 84, of moderate volume and tension. Respirations 26. Tongue slightly furred. On examining the abdomen the liver could be felt a little below the costal margin, but the upper limit of hepatic dulness appeared to be in about the natural position. The spleen was not felt. There was a little œdema in the lower part of the legs, but none at the loins. The handwriting was somewhat tremulous. About this time I thought there was evidence of wasting in the pectoralis major muscle on each side. The biceps muscles and the

thenar eminences likewise appeared relatively small. There was, however, no very marked muscular atrophy anywhere. Dr. F. E. Batten (July 18th, 1900), who kindly examined the patient, found the reaction to faradism in the muscles of the upper extremities and hands fairly good, but the current on that occasion was not strong enough to test the reactions to galvanism. He thought the patient's shoulders appeared thickened. Nothing abnormal was discovered in regard to sensation (for heat and cold, etc.). Knee-jerks active and equal. No ankle-clonus. Plantar reflexes natural. The patient at that time apparently suffered no pain, and there was no special tenderness on tapping any part of the cranium or vertebral column. The hot weather seemed to give the man greater freedom of movement. Later on (August) an ophthalmoscopic examination (one eye only) was made, but with negative results.

At the commencement of September Dr. Batten kindly made another electrical examination, and reported—"All the muscles of the arm and hand react to faradism, but they require a strong current in order to make them contract well The muscles react badly to galvanism; it requires a strong current in order to get a contraction. There is very little difference between the KCC and ACC; the former appears, however, to be somewhat the stronger."

A blood examination on July 18th, for which I am indebted to Dr. Drysdale, gave the following results:—Red cells 3,214,000 in the cubic millimetre; total leucocytes 12,000; of the leucocytes the lymphocytes constituted 34·7 per cent., the large mononuclear 7·1 per cent., the polymorphonuclear 56·2 per cent., the eosinophile 2 per cent.; there were no myelocytes. Conclusions:—Slight leucocytosis; all forms proportionately increased; slight anæmia.

On July 12th, 1900, the nature of the proteid in the urine was first recognised. On this occasion a microscopic examination was made of the sediment collected by the centrifuge from a specimen of the urine which had

been allowed to stand for some time. It contained hyaline casts,[1] some of them sprinkled with granules or containing cells; also a few round cells and one or two oxalate of lime crystals.

From this time until the patient's death the urine was examined at various intervals, and was always found to give typical reactions for the Bence-Jones proteid. The specific gravity varied apparently from about 1012 to 1020. Sugar was tested for on different occasions, but with a negative result. No Gerhardt's reaction (perchloride of iron test) was obtained. Sometimes the patient's urine, as already mentioned, was turbid when freshly passed,[2] evidently with what Dr. Bradshaw believes to be a spontaneous precipitate of the Bence-Jones proteid. This was notably the case when, at Dr. Bradshaw's suggestion, a few small doses of benzoate of ammonium had been previously given and the reaction of the urine was very acid. Dr. Bradshaw considers the spontaneous precipitate to be the proteid, because "when it has been separated out by the centrifuge and suspended in a little water, it is almost entirely dissolved by a little caustic soda and thrown down again by nitric acid."[3]

Dr. R. Hutchison kindly undertook a quantitative examination of the Bence-Jones proteid in the patient's urine. The urine passed during forty-eight hours (July 24th to 26th, 1900) was carefully collected and sent to him. His report is as follows:

[1] A later microscopical examination (August 9th, 1900) confirmed the presence of hyaline casts in the urine. On the other hand, Dr. R. Hutchison found casts absent in a specimen examined by him at the end of July, 1900.

[2] The spontaneous precipitate appeared sometimes to occur, not before the urine was passed, but soon afterwards.

[3] To find out more carefully whether a sediment consists entirely or partially of the Bence-Jones proteid, Dr. Bradshaw recommends the following:—"Draw it off with the pipette and reduce it to a small bulk on the centrifuge. Shake it up with water containing a trace of acetic acid (to dissolve any phosphates present), and centrifugalise again. This washing may be repeated. Collect the deposit on a filter and extract it with 0·2 per cent. caustic soda." The filtrate should give the usual reactions for the Bence-Jones proteid.

The urine was pale in colour, of specific gravity 1020, faintly acid in reaction, and somewhat more viscid than normal. There was sometimes a slight amorphous whitish deposit containing a few crystals of oxalate of lime. There were no casts.

The urine contained about 0·83 per cent. (estimated by precipitate with alcohol, drying and weighing) of a proteid which separated out in flocculi at a temperature of 58° C. On boiling, the precipitate disappeared, in some specimens entirely, reappearing on cooling; in others it gathered into a viscid mass which floated on the top.

Nitric acid gave a precipitate which disappeared partially on heating, and reappeared on cooling.

Strong HCl gave a distinct ring with the urine diluted 1 in 20 (Bradshaw's reaction).

Acetic acid alone gave no precipitate. On the addition of potassium ferrocyanide solution an immediate but not very abundant precipitate appeared.

The proteid separated out slowly on prolonged contact with NaCl in excess; NaCl + acetic acid caused a rapid separation.

In some specimens the proteid was precipitated by half-saturation with ammonium sulphate, in others only when the salt was added in slight excess.

No precipitate appeared on dropping the urine into an excess of distilled water, and it was only partially precipitated on prolonged dialysis.

On digestion with pepsin-HCl a considerable residue was left.

On an average about 15 grammes of the substance were excreted daily, and the urine contained no other proteid.

The total phosphates were estimated on two days with following results:

Total P_2O_5.	*Earthy* P_2O_5.
1. 1·173 grammes.	0·890 gramme.
2. 1·860 grammes.	

Dr. Hutchison added that the total of phosphates excreted was low, but the ratio of earthy to alkaline phosphates was high. He likewise collected some of the pure Bence-Jones proteid from the urine and found it to contain no phosphorus. In this respect, he pointed out, his results agreed with those in most previous cases.

I endeavoured on one occasion to find out whether an alteration in the diet of the patient would produce a corresponding alteration in the amount of the Bence-Jones proteid excreted in his urine. For two days (July 26th to 28th, 1900) the patient abstained from

meat, fish, and eggs, taking bread, butter, milk, and milk pudding. During the last twenty-four hours on this diet the patient passed 2100 c.c. of urine, which the rough test by Esbach's tube showed to contain 7 per mille proteid. Therefore the patient continued, in spite of the alteration in diet, to pass about 15 grammes of the Bence-Jones proteid in twenty-four hours.

The patient's general condition apparently remained stationary for a considerable time after leaving the hospital in July. Keeping the bowels open, and a saline diuretic medicine, seemed to suit him best. In December, however, he rapidly lost ground, and was re-admitted December 27th, 1900.

Notes after re-admission.—The patient has become much weaker, and has wasted much (weight on December 27th, 1900, 67½ kilogrammes). The loss of power in the upper extremities has remained about the same. The right arm can be moved more than the left one. There is marked wasting of supraspinatus, infraspinatus, and biceps muscles on each side, and there seems to be some enlargement of the head of each humerus. There is likewise an abnormal "tapering" of the fingers, and the fleshy cushions in front of the terminal phalanges appear somewhat shrivelled. There is a spotty pigmentation of the skin of the hands. No anæsthesia can be detected.

The patient says that four of his teeth were so loose that he removed them with his own hand two weeks before re-admission. After re-admission several other teeth were found to be loose, and the tongue was swollen and indented and ulcerated, the ulcers corresponding to irritating teeth. There was some bronchitis, with muco-purulent expectoration, and slight impairment of resonance at the base of one lung. Dyspnœa on slight exertion. Temperature never up to 100° F. The liver and spleen could not be felt. No ascites; no œdema of the lower extremities. Attached to one of the ribs on the right side of the back, about the level of the inferior angle of the scapula, a little hard, rounded projection, of about the

size of a large cherry, was noted, not painful or markedly tender on pressure. This was, I think, in the ordinary position for one of the projections which in some individuals can be seen marking out the angles of the ribs and the tendinous structures connected with them.

Urine.—During twenty-four hours (December 29th to 30th, 1900) patient passed 1300 c.c. of urine, of sp. gr. 1016, and neutral reaction, slightly turbid with phosphates; in this urine one or two casts were detected under the microscope. During the next twenty-four hours (December 30th and 31st) patient passed 1500 c.c. of urine, of sp. gr. 1016, neutral in reaction, clear, and apparently free from casts. Gerhardt's reaction (with perchloride of iron) was negative on both days. The urine from these two days was sent to Dr. R. Hutchison, who kindly examined it, and found that it resembled the previous specimens:—"It gives all the reactions of Bence-Jones proteid, as set forth by Magnus-Levy.[1] In addition, it gives Bradshaw's hydrochloric acid reaction quite distinctly. The patient is excreting about 16 grammes of the substance daily, and about 1·5 grammes of P_2O_5."

Patient's teeth were attended to and some loose ones removed. The ulcers over the front of the tongue (local treatment by chromic acid solution, etc.) apparently got better, but there was a bad one at the back, and the tongue felt hard and infiltrated. The lingual condition then seemed to be gummatous, as Dr. Bradshaw suggested when he saw the case. Iodide of potassium was accordingly prescribed, and quinine was likewise given. Under this treatment the condition of the tongue apparently improved somewhat. The pulse was generally between 90 and 100, and respiration between 30 and 36.

On the evening of January 24th, 1901, severe hæmorrhage from the bowel occurred, causing a state of collapse. With camphor hypodermics and inhalation of oxygen

[1] Loc. cit.

there was temporary improvement, but on the evening of January 25th patient died quietly.

An examination of the blood kindly made by Dr. Drysdale on January 21st, 1901, had given the following results :—Hæmoglobin, 23 per cent. of the normal ; red cells, 2,980,000 in the cubic millimetre ; total number of leucocytes, 11,000 ; of the leucocytes, the lymphocytes constituted 25·6 per cent., the large mononuclear 3 per cent., the polymorphonuclear 70·3 per cent., the eosinophile 1 per cent. ; there were no myelocytes or atypical cells seen in 300 leucocytes counted. Conclusions : slight leucocytosis ; no special change. Dr. Drysdale added that owing to running over in von Fleischl's apparatus the hæmoglobin was possibly estimated at slightly too low a value.

Necropsy and Pathological Examination.

The necropsy was performed on January 26th, 1901, about sixteen hours after death. For convenience I shall arrange the results of the whole pathological investigation under the following headings :

1. The mouth and alimentary canal.
2. The other abdominal viscera.
3. The thoracic viscera, etc.
4. The nervous system and muscles.
5. The joints, tendons, etc.
6. The skeleton and myelomatous growth.
7. The chemical examination by Drs. Hutchison and Macleod.

1. *The Mouth and Alimentary Canal.*

The tongue was ulcerated and hardened, apparently from a diffuse inflammatory infiltration or from new growth. Microscopic examination showed the presence of a diffuse gummatous change. It is perhaps worthy of

remark that in sections of the tongue stained with methyl violet a good deal of amyloid (lardaceous) or closely allied substance [1] was found, though none was discovered in similarly stained sections of the liver, spleen, and kidney. In an article on "Syphilis and Lardaceous Disease" [2] in 1895 I drew attention to the occasional localisation of amyloid changes about syphilitic gummata.

Nothing noteworthy was observed in the stomach, but there was a rather deep chronic ulcer in the duodenum close to the pylorus, and this was doubtless the source of the blood passed from the bowels during life. The intestines contained blackish material, the colour doubtless being due to altered blood.

2. *The other Abdominal Viscera.*

The *liver* was rather large, weighing 78 ounces, but its substance neither macroscopically nor microscopically showed anything noteworthy. The *gall-bladder* contained green bile. There were no gall-stones. The *pancreas* showed nothing abnormal. The *spleen* weighed about six ounces; sections under the microscope showed the presence of a good deal of pigment.

The *kidneys* looked rather pale, but it must be noted that most of the organs appeared somewhat bloodless, doubtless owing to the poorness of the blood in hæmoglobin and to the profuse intestinal hæmorrhage preceding death. Both kidneys together weighed about twelve ounces. The capsules were partially adherent, the cortex had a slightly granular surface, and there were one or two cysts. Under the microscope a moderate amount of fibrotic change (chronic interstitial nephritis) was ob-

[1] If the substance in question was not actually amyloid, it was a very closely allied body, as the rosy coloration with methyl violet proved. It was certainly much nearer to amyloid than to hyaline substance. The muscular coats of the small blood-vessels were, however, as yet not quite characteristically picked out.

[2] 'American Journ. Med. Sciences,' November, 1895.

served, explaining the presence of hyaline casts in the urine during life.

The *adrenals* appeared normal. The *mesenteric glands* were not specially large. No chalky deposits were discovered in the kidneys or other organs, such as Virchow has described ('Kalk-Metastasen') in cases where bony tissue has been rapidly destroyed by malignant neoplasms, and such as were found in the kidneys in Stockvis's case of multiple myeloma with Bence-Jones proteid in the urine (see Case No. 4 in the summary). A few such were noted in my case of multiple myeloma examined in 1897, which in some respects clinically resembled the present case, though there was probably no Bence-Jones proteid in the urine.[1] It must be remembered, however, that in the last-mentioned case the bone had been destroyed more rapidly and to a much greater extent than in the present case. Moreover, some of the microscopic calculi were situated in the neighbourhood of minute cystic adenomata of the kidney, and I have reason to believe that they may accompany renal adenomata in persons who are quite free from any bone disease. Very similar bodies were mentioned by Charles Sabourin in his well-known paper on multiple adenomata in cirrhosed kidneys,[2] and they were present likewise in the case of "papillary adenoma of the kidney" which I recorded in

[1] 'Transactions of the Pathological Society of London,' 1897, vol. xlviii, p. 169; and 'Journal of Pathology,' January, 1898. I shall have to refer to this case later on in greater detail. Only one entry on the urine could be found in the notes. It said that there was "no albumen." The house physician who examined the urine might just possibly have overlooked the presence of Bence-Jones proteid, as in testing for albumen he frequently used only the potassium ferrocyanide and acetic acid test, and Dr. Bradshaw, using this test in his case, found that no turbidity was produced at first unless a large excess of the acid was added, though after several minutes the turbidity gradually appeared. Judging, however, from the reaction in J. T—'s urine, which was fairly rapid to the ferrocyanide test, I think it very unlikely that any such mistake occurred.

[2] 'Revue de Médecine,' Paris, 1884, p. 446.

the 'Transactions of the Pathological Society of London,' 1898.[1]

3. *The Thoracic Viscera, etc.*

The *heart* weighed thirteen ounces. The inner surface of the left auricle was hard and very rough, evidently the result of a former extensive endocarditis. The mitral, aortic, and pulmonary valves were not diseased, but there was some irregular thickening of the tricuspid valve. The *pericardium* contained about two ounces of clear serous fluid. There was much atheroma of the *thoracic aorta*. There was evidence of *bronchitis*, and portions of the lung substance appeared collapsed. There was no pleuritic effusion. Some pigmented and moderately enlarged *mediastinal glands* were observed. The *thyroid gland* macroscopically and microscopically showed nothing abnormal.

4. *The Nervous System and Muscles.*

The brain weighed about fifty-four ounces. The membranes were slightly thickened. Dr. F. E. Batten kindly undertook the examination of the brain, spinal cord, a part of the left brachial plexus, and the nerves and muscles of the right hand, that in which the loss of power and tremor had been most marked during life. Following is Dr. Batten's report:

"The brain and spinal cord were examined by the Nissl, Marchi, Weigert-Pal, and van Gieson methods. Nothing abnormal could be detected except that the cells of the anterior horns contain an abnormally large amount of pigment granules.

"*The peripheral nerves.*—With regard to the peripheral nerves, nothing abnormal could be detected either in the ulnar, radial, or median nerves, either in section or in the teased specimens.

[1] Vol. xlix, p. 177.

"*Muscles.*—The small muscles of the hand examined were the abductor minimi digiti and the abductor pollicis. By the Marchi method the muscle-fibres appear to be normal both on longitudinal and transverse section. By the van Gieson method the greater part of the muscle appears to be normal; in one bundle, however, there is an increase of the nuclei of the sheath of the fibres. The fibres themselves are about the natural size, and their transverse striation is normal."

5. *The Joints, Tendons, etc.*

One hip-joint and one shoulder-joint were examined, and showed no destruction of articular cartilage, but showed a certain amount of "lipping," much capsular thickening, and excessive villous growth and formation of pendulous bodies from the synovial membrane. The wrist-joint and the metacarpo-phalangeal joints of the right side were likewise examined; they showed similar alterations. In some of them synovial fringes projected between the opposing articular cartilages, partially separating them from each other. The whole condition resembled one of rheumatoid arthritis. The lump noted during life on the posterior portion of one of the ribs was examined and found to be an early gummatous formation in the tendinous structures at one of the costal angles.

6. *The Skeleton and Myelomatous Growth.*

The vertebral centra, the ribs, the sternum, part of the skull, and some of the bones of the extremities were examined. The bone-marrow and cancellous tissue were found more or less uniformly infiltrated by tumour growth. It is not too much to say that the whole skeleton was more or less involved, even the diploë of the skull and the marrow of the terminal phalanges of the fingers. The softening and yielding of some of the dorsal vertebræ, consequent on the tumour formation, were the cause of

the progressive kyphosis noted during the patient's life. The body of one of the vertebræ was so altered in shape that in a sagittal section it appeared as a triangle with its apex towards the front of the body, wedged in between two centra which might comparatively be said to have retained their normal shape. In some parts the bone-marrow and cancellous tissue seemed to have completely given place to the new growth. Thus, much of the interior of the manubrium sterni was occupied by a soft tumour mass from which all bony matter had disappeared. Nowhere, however, even in the ribs and sternum, had the tumour given rise to any external protuberances, such as have been recorded in some cases of multiple myeloma; and nowhere had it led to the occurrence of fractures. On the whole, far less absorption of bony substance had taken place than in my case of multiple myeloma (without Bence-Jones proteid in the urine) examined in 1897.[1] In that case the ribs had been converted into thin-walled tubes filled with soft growth, and in some places the periosteum and bony shell had been bulged out by the tumour; many spontaneous fractures had occurred, and one of the vertebral centra was almost entirely replaced by diffluent new growth.

In the present case, as in the case just alluded to, the new growth seems to have commenced in different parts at the same time, and it is impossible to pick out any portion of the tumour as being the primary growth. If the tumour be termed myeloma the whole process may, for this reason, justly be termed "myelomatosis."

Some portions of the growth are quite pale, others deep red. This redness of certain portions is seen by microscopic examination to be due to a large amount of blood not contained in blood-vessels, but lying free amongst the tumour cells.

The growth consists chiefly of mononuclear rounded or polyhedral cells, the characteristic of which, by the ordinary methods of staining, is that many of them are

[1] 'Trans. Path. Soc.,' loc. cit.

crammed full of globules, and that these globules stain with eosine almost exactly like red blood-corpuscles. They seem, indeed, at first sight to be red blood-corpuscles included in the tumour cells, though they vary greatly in size, some being much larger and some smaller than ordinary red cells. But, on examining specially stained preparations, another explanation of the appearance, one suggested to me by Professor R. Muir, of Glasgow, becomes far more probable. He has examined the growth and has kindly sent me a report, which I shall now quote :

"I have examined the tissue carefully, after staining in various ways, and have come to the following conclusions :—It may be said to have the general characters of a sarcoma, and its vessels resemble more closely those of a sarcoma than those of the marrow. It is composed of practically one variety of rounded cell, which presents certain resemblances to the neutrophile myelocyte, from which, however, it differs in the relatively smaller size of the nucleus and in the more abundant protoplasm. In the protoplasm, moreover, there can be shown a large number of granules which vary considerably in size, but the smallest and most abundant of which are distinctly larger than the neutrophile granules. With hæmatoxylin and eosine these smallest granules are practically unstained by the eosine ; with Ehrlich's tri-acid they are coloured, but have not quite the same tints as the neutrophiles, the staining being of a dirty brown colour ; with Mann's eosine-methyl-blue combination [1] they are stained

[1] Dr. Gustav Mann's stain was first published in 'Proceedings Scottish Microscop. Society,' 1893-4, p. 165. The method is likewise described in full in a paper by Copeman and Mann on the "Histology of Vaccinia" ('Annual Report of the Medical Officer of the Local Government Board,' 1898-9, p. 509).—The description is as follows :

"*Mann's Bi-acid Mixture of Methyl Blue and Eosine.*

"1 per cent. methyl blue in distilled water	35 c.c.
1 per cent. eosine in distilled water	45 c.c.
Distilled water	100 c.c.

"Sections are left in this mixture for five to ten minutes, washed in

bright red with a slightly violet tint (whereas the neutrophiles are unstained) ; with Unna's polychrome methylene blue the granularity is faintly visible, but the granules are not really stained. We may therefore say that they have, on the whole, a more distinctly (though not a pure) oxyphile reaction than the neutrophile granules. Only a very small proportion of the cells appear to be without granules. In addition, however, to these small granules, many larger ones are present, and all intermediate sizes can be found up to large rounded bodies as large as, or even larger than, ordinary red corpuscles. I thought at first that these rounded bodies were included red corpuscles, but, on more careful examination, I believe that they are formed by the confluence of smaller globules. Some of them also are seen lying free. They are more distinctly oxyphile than the smaller granules, and stain with eosin by the ordinary methods. It is also to be noted that the rounded bodies lying free stain with the tri-acid stain of a different tint from the red corpuscles ; further, they always seem to be

water, dehydrated, and mounted in balsam. This constitutes what may be termed the 'short method.' Or they are dealt with by the 'long method,' *i. e.* are left in the stain twelve to twenty-four hours, then washed in distilled water, thoroughly dehydrated, and placed in a vessel containing absolute alcohol 30 c.c., to which previously five drops of a 1 per cent. solution of KHO in absolute alcohol have been added. When the sections have turned a reddish tint, the slide is washed with absolute alcohol to remove the alkaline alcohol, then rinsed in distilled water till differentiated. If the sections are not blue enough, a drop of acetic acid added to the water in which they are being rinsed will restore the colour."

Professor Muir used Mann's long method without any other stain afterwards. Some sections stained by Ehrlich's acid hæmatoxylin after Mann's long method gave the large globules in the tumour-cells a slightly different tint. When the sections had been stained according to the preceding directions, they were passed through water into Ehrlich's acid hæmatoxylin, and after having been kept there from one half to two minutes, they were washed in tap water, dehydrated, and mounted in the usual way. For preparing sections from this case, and from two other cases of myelogenic growth, I am much indebted to Mr. E. H. Shaw.

perfectly spherical in form. I should also have mentioned that in the tumour-cells there is often a narrow zone around the nucleus which is comparatively free from granules.

"I accordingly consider that the tumour is formed by a special and characteristic type of cell, which is probably derived either from the neutrophile myelocyte or its predecessor; that this cell produces in its protoplasm in a granular form a substance which is closely allied to, though not quite identical with, the substance of the neutrophile granules; and that this substance is formed in excess, and may form larger granules by confluence of the smaller, the larger globules sometimes becoming free."

According to J. H. Wright's report on a case examined by him,[1] the principal tumour-cells in the case in question appeared to be a variety of Unna's "plasma-cells." Dr. J. M. H. MacLeod has kindly examined sections from the present case to compare the cells with Unna's plasma-cells. He has used the special methods of staining for this purpose, and tells me :—"Morphologically the cells resemble plasma-cells in that they are polyhedral and their nucleus is placed excentrically. The nuclei, however, do not show the characteristic arrangement so generally found in plasma-cells of five or six deeply stained chromatin bodies around the periphery."

Since receiving Professor Muir's report I have examined a number of sections from the sternum stained by Mann's method and by Ehrlich's tri-acid stain (see Plate IV). There is a sprinkling of small cells, resembling lymphocytes, with round nucleus and little protoplasm; but with this exception the growth is practically composed of the same kind of cells as those mentioned as characteristic in the parts from which Professor Muir made his report. Some of the larger globules referred to by Professor Muir are two or three times as large as ordinary red corpuscles, and a good number of

[1] 'Johns Hopkins Hospital Reports,' 1900, vol. ix, pp. 359—366. (See Case No. 13 in the summary of cases at the end of the present paper.)

them are free, lying singly or in groups amongst the tumour-cells. The globules of about the same size as red corpuscles are, however, more numerous, and are mostly enclosed in tumour-cells or arranged in clusters as if those of each cluster had been formed in a single cell and were still united together in some way. Such clusters often consist of a dozen or more globules, and sometimes resemble mulberries or bunches of grapes.

By Mann's method the *globules* in question are not all stained exactly alike. Sometimes they are stained quite like the red blood-corpuscles are, but generally they take on a distinctly more violet or brownish-violet colour, and this is especially the case in sections which I had stained with Ehrlich's acid hæmatoxylin [1] after Mann's eosin and methyl-blue combination. On the other hand, the *smaller granules* are less well stained when the sections are treated for shorter lengths of time in the alkaline alcohol, when acetic acid is not used and when hæmatoxylin is likewise employed.

Red corpuscles (taking on the eosin stain), if they were included in the tumour-cells (stained blue), would also appear violet in colour, and in some pathological conditions the red corpuscles vary greatly in size and do not all stain alike. The globules in the present tumour tissue are, however, distinguished from red corpuscles not only by their great variation in size and by their reactions to special stains, but also by their being spherical in shape. Moreover they are, if anything, best seen in the paler parts of the growth, where there are fewer red blood-corpuscles.

We may conclude that the granules and globules of different sizes, which constitute a characteristic feature of the tumour-cells in the present case, are probably all of the same nature, though they vary almost as much in size as do fat globules [2] in a fatty liver. Some of the tumour-

[1] See the foot-note about Mann's stain.

[2] In fact, if it were not for their reactions, one might suppose that all these globules were fat. Owing, however, to the method employed in

cells appear tightly packed with medium-sized globules, others contain one or two larger globules, quite three times as large as ordinary red blood-corpuscles. A good many of the larger globules can be seen lying free amongst the tumour-cells, as if they had been cast off or had been set free by the disintegration of the cell in which they were originally found.

At the end of his report Professor Muir suggested a possible relationship between the granule and globule formation in the tumour-cells and the excretion of Bence-Jones proteid in the urine. The view that the globules may represent a stage in the formation of the proteid in question is supported by the consideration that during the life of the patient these globules were probably being produced in *all* the bones of his body. Further investigation in other cases will doubtless throw more light on the question. If, however, these globules are in any way connected with the Bence-Jones albumosuria, why have they not been discovered in the microscopical preparations from other cases? It is, perhaps, worth mentioning that in the present case the tissues were at once put into weak formalin, where some of them were kept for several months before sections were cut.[1]

7. *The Chemical Examination by Drs. R. Hutchison and J. J. R. Macleod.*

For examination they had—

a. Blood and clots from heart, etc.

b. Clear serous fluid from pericardium.

preparing the sections (embedding in paraffin), all true fat would have been dissolved out. Professor Muir tells me that the granules in the growth may possibly be chemically related to vitelline granules, and he thinks that their staining reactions correspond with those of the zymogen granules of the pancreas, but he has stated in his report what he believes to be the most probable source of such granules in the marrow.

[1] A 4 per cent. aqueous solution of formalin slowly precipitates the Bence-Jones proteid from the urine.

c. Parts of ribs, spinal column, and long bones.

d. Parts of liver, spleen, kidneys, and striped muscle.

In their report they at first recapitulate the chemical reactions of the proteid in the patient's urine, and then give an account of their chemical examination of the tissues obtained at the necropsy.

The Chemical Reactions of the Body in the Urine.

Several samples of the urine were furnished us, in which we employed most of the reactions described by previous writers.[1] The following were the chief results obtained:

1. *Heat coagulation.*—A coagulum appeared at about 58° C. In one of the samples this coagulum disappeared entirely on boiling, returning on cooling. In two other samples, however, the coagulum did not clear up entirely on boiling, but the diffuse coagulum collected itself into flocculi on the surface of the liquid.

2. *Nitric acid.*—The addition of 25 per cent. nitric acid produced a coagulum which cleared up partially on boiling, becoming again more distinct on cooling. By employing Heller's method a sharp ring was obtained, which became less distinct on carefully warming the test-tube.

3. *Hydrochloric acid.*—This was employed by the method described by Bradshaw (namely, pouring the urine diluted twenty times on to the surface of the acid), and a very distinct ring was obtained.

4. *Potassium ferrocyanide and acetic acid.*—A slight precipitate was obtained, which became less distinct on boiling.

5. *Saturation with common salt and the addition of acetic acid.*—A rapid and abundant precipitate was produced.

6. *Half-saturation with ammonium sulphate.*—In one sample this produced complete precipitation of the body, the filtrate being proteid-free. In two samples, however, this amount of the salt did not effect complete precipitation, a much larger quantity being necessary to produce that result. The addition of two volumes of a saturated solution of ammonium sulphate produced complete precipitation. This precipitate was collected on a filter-paper, washed

[1] Bence-Jones, 'Philosoph. Transact. Roy. Soc.,' 1848, part 1, p. 55; Hüppert, 'Prager med. Wochenschr.,' 1889, S. 35; Kühne, 'Zeitschrift f. Biolog.,' 1883, Bd. xix, S. 209; Matthes, 'Verh. d. 14 Congresses f. innere Medicin,' 1896, S. 476; Ellinger, 'Deut. Arch. f. klin. Med.,' 1899, Bd. lxii, S. 255; T. R. Bradshaw, 'Med.-Chir. Trans.,' vol. lxxxi, p. 259; Kalischer, 'Deut. med. Wochenschr.,' 1901, S. 54.

with a saturated solution of ammonium sulphate, and dissolved by adding water. The resulting solution was dialysed for several days. The dialysate was slightly opalescent and gave the following reactions:

On heating, a coagulum was obtained at 66° C., which cleared up entirely at 90° C. After the addition of one drop of 20 per cent. acetic acid to 20 c.c. of the fluid, the coagulum appeared at 50° C., and also cleared up at 90° C. Nitric and hydrochloric acid tests as above. Two volumes of saturated common salt solution with a few drops of acetic acid gave a copious precipitate. Acetic acid and potassium ferrocyanide gave a precipitate which cleared up considerably on heating. On boiling for some time with hydrochloric acid a distinct violet colour was produced, which was probably due to some chromogens present in the dialysate. Boiling with nitric acid did not produce this effect.

7. *Alcohol.*—Complete precipitation was produced by adding 2 vols. 96 per cent. alcohol. The precipitate was soluble in weak ammonia.

8. *Acetic acid.*—No precipitate.

9. *Neutralisation with sodium hydrate or ammonia.*—No precipitate.

10. *Neutralisation with caustic soda after strongly acidifying with acetic acid.*—No distinct precipitate.

11. No precipitate was produced by dropping the urine into an excess of distilled water.

12. A sample of urine was dialysed for several days. There was a slight precipitate, which was not proteid in nature. The dialysate gave all the above reactions.

From a *consideration of the above results* it is evident that the case was a typical one of Bence-Jones albumosuria. *No albuminuria* was present, as the urine was rendered proteid-free by the addition of twice its volume of a saturated solution of ammonium sulphate. *No globulin* was present, since no proteid separated out from the urine on dialysis. The precipitate obtained by the addition of 2 vols. saturated ammonium sulphate solution was dissolved by adding water, and was then subjected to dialysis for several days. After this it was reprecipitated in the dialysate by the addition of alcohol; the precipitate was filtered off, washed several times with alcohol, and tested for phosphorus (after fusion in a silver basin with saltpetre and caustic soda), with a negative result. This proves the *absence of nucleo-proteid.*

The Chemical Examination of the Organs.

Up to the present time only three cases have been recorded in which a chemical investigation of the organs was made.

The first of these is by Ellinger,[1] but the clinical history of the case shows it to have been of an unusually acute nature, and the symptoms scarcely typical of myelogenous disease.

The tissues examined were a piece of infiltrated rib, blood, and some ascitic fluid.

In the case of the piece of rib, the following somewhat rough method was employed. The piece of rib was macerated with water, the resulting extract was filtered off, and to part of it was added some sodium chloride and acetic acid, whereby a precipitate was produced. In another part of the watery extract the point of heat coagulation was determined and found to be 40° C.

The author mentions that a piece of normal rib-marrow treated in the same way does not give these reactions.

In the case of the blood and ascitic fluid, a more reliable method was employed.

To each was added an excess of alcohol, and the resulting precipitate was allowed to stand several days. It was then filtered off and macerated with water. The resulting watery extract was then weakly acidified with acetic acid and boiled. The boiling fluid was quickly filtered, so as to separate all coagulated proteid, and the filtrate, at first quite clear, gradually became cloudy on cooling, and gave the reactions for Bence-Jones proteid.

The second case is recorded by Askanazy,[2] and is peculiar in that an examination of the blood during life, and of the lymphatic glands after death, showed it to be one of lymphatic leukæmia.

The tissues examined were marrow from the vertebræ and head of femur, lymphatic tumours, blood, pericardial and pleuritic fluids.

Two methods were employed in testing for the proteid. One of these consisted in making a watery or weak caustic soda extract of the tissue. This was then treated with acetic acid, so as to precipitate nucleo-proteid, which was filtered off. In the filtrate the heat-coagulation point was determined. It was then boiled and filtered hot, the resulting filtrate being gradually cooled. The other method consisted in adding alcohol to the extract, collecting the precipitate, and macerating it with weak caustic alkali. The resulting extract

[1] 'Dent. Arch. f. klin. Medicin,' 1899, Bd. lxii, S. 255. (See Case No. 9 in the Summary.)

[2] Ibid., 1900, Bd. lxviii, S. 34. (See Case No. 16 in the Summary.)

was then treated with acetic acid to precipitate nucleo-proteid, and to the filtrate from this were applied the tests for Bence-Jones proteids.

By means of these methods it was found that the Bence-Jones proteid was present in the marrow, but absent from the lymphatic tumours, blood, and pericardial and pleuritic fluids.

The alcohol method was employed in a sample of urine containing the albumose, and was found to give reliable results.

The third case is that of Kalischer,[1] and the tissues examined were marrow from the ribs and humerus. The examination was made by Prof. Löwy, but he could not find a trace of Bence-Jones proteid.

Methods employed in the present case.—In the present case a very complete chemical investigation was possible, as we were fortunate in securing not only portions of all the organs, but also large qnantities of bone from various regions.

Two methods, very similar to those described by Magnus-Levy, were employed to detect the body.

The bones were crushed into fragments in a quartz crusher, the other tissues being chopped up into small pieces. Each was then ground up in a mortar with distilled water, and the resulting pulp allowed to stand twenty-four hours. The extract was filtered off, and the remainder again pounded in the mortar with distilled water, the second extract, after filtration, being added to the first

The resulting watery extract from each tissue was then carefully neutralised and divided into two equal parts. To *one* of these were added two volumes of a saturated solution of ammonium sulphate, and the mixture allowed to stand twenty-four hours. The resulting precipitate was separated by filtration, washed with ammonium sulphate solution, and suspended in water. After standing several days this suspension was filtered, and the filtrate placed in a parchment dialyser, for several days in running water, and finally for at least two days in distilled water, which was frequently changed. After dialysis, a precipitate invariably separated out (globulin), which was removed by filtration. The resulting filtrate was tested for Bence-Jones proteid. To the *second* portion of the neutralised watery extract twice its volume of spirit was added, and the mixture was then boiled (by which means the native proteids become coagulated, whereas the Bence-Jones proteid does not).[2] The mixture was then filtered, and the precipitate, after being washed with

[1] 'Deutsch. med. Wochenschr.,' 1901, No. 4, S. 54. (See Case No. 22 in the Summary.)

[2] Magnus-Levy, Hoppe-Seyler's 'Zeit. f. phys. Chemie,' 1900, Bd. xxx, S. 200.

boiling 66 per cent. spirit, was suspended in ¼ to ½ per cent. ammonia, and either left in this for several hours or heated on the water-bath (by either of which processes a solution of the albumose results, while the coagulated proteids remain unaffected).

The former of these methods we will designate the ammonium sulphate method, the latter the alcohol method.

These two methods were applied to urine containing the substance in question. The resulting solutions gave the chief reactions for Bence-Jones proteid (see first part of report).

To serve as controls we also examined, by both methods, red marrow from the vertebræ of a healthy person, and by the ammonium sulphate method, red marrow from the ribs of a horse. *In neither of these was any trace of Bence-Jones proteid* [1] *found.*

Results.—The following are the results obtained from the various organs and tissues:

Marrow of Bones.—The marrow contained in these was apparently of two types—namely, a pink pasty mass in the head and lower extremity of the femur and in the ribs, and a thin red-currant-jelly-like mass in the shaft of the femur. We therefore divided the bones into three groups, viz. (1) vertebræ and ends of femur; (2) ribs; and (3) shaft of femur.

1. *Vertebræ and ends of femur.*—The neutralised extract by the alcohol method was very opalescent, and could not be cleared by filtration. It was accordingly dialysed for three days in tap water, and for twenty-four hours in distilled water. A slight precipitate separated out, and on filtration a clear solution was obtained. In the dialysates by both methods the following reactions were obtained:

Heat coagulation.—A coagulum was obtained at 70° C., which did not clear up on boiling. On filtering the boiling fluid, the filtrate did not show any opacity on cooling. On the addition of one drop 20 per cent. of acetic acid to 30 c.c. of the fluid, coagulation occurred at 50° C., but the precipitate did not clear up on boiling, although it appeared to do so to a certain extent because of the coagulum separating out as flocculi on the surface.

Hydrochloric acid.—A distinct sharp ring was obtained.

Nitric acid.—A similar ring was obtained, which cleared up considerably on heating, reappearing on cooling.

[1] In the case of the red marrow from the horse's rib, the extract by the ammon. sulph. method contained a *trace* of albumen coagulating at 75° C. In the case of the human vertebræ by the alcohol method, the application of the nitric and hydrochloric acid tests produced an indefinite haze but no distinct ring, and no coagulation occurred on heating even to boiling temperature.

Two volumes of a *saturated solution of common salt and a few drops 20 per cent. acetic acid.*—A precipitate.

A few drops *acetic acid and potassium ferrocyanide.*—A precipitate, not clearing on boiling.

Biuret test.—Violet reaction.

In the opalescent solution by the alcohol method the addition of one drop 20 per cent. acetic acid produced a precipitate, soluble, however, in excess of the acid.

2. *Ribs.*—By the alcohol method an opalescent fluid was obtained, which gave a very distinct precipitate on the addition of acetic acid. The opalescent fluid was dialysed for several days and filtered.

The clear fluid by both methods gave the following reactions:

Heat coagulation.—Slight haze at 60° C., which did not clear up on boiling.

Nitric and hydrochloric acids.—A distinct ring was obtained with both of these reagents, which cleared up considerably on boiling, becoming more distinct on cooling. A slight haze was produced by adding 1 in 10 HCl to the fluid.

Acetic acid 20 per cent.—A few drops of this produced a distinct precipitate insoluble in excess.

Biuret test.—Slight violet reaction.

The precipitate produced in the undialysed opalescent solution by the alcohol method on the addition of acetic acid[1] was fused in a silver basin with caustic soda and saltpetre; the resulting mass was dissolved in water, acidified with nitric acid, and mixed at 60° C. with ammonium molybdate solution. No trace of phosphorus was found present.

3. *Shaft of femur.*—The extracts contained only the merest trace of a proteid, and the only reactions which gave anything were the ring tests.

4. *Kidneys.*—Slight rings were obtained with the acids, and on boiling the fluid became opalescent.

5. *Liver.*—No trace of proteid was shown by any reaction by either method.

6. *Spleen.*—Same result.

7. *Muscle.*—Same result.

8. *Pericardial fluid.*—Slight rings were obtained with the acids, and on boiling an opalescence was produced. Acetic acid produced no haze. The ammonium sulphate method was alone employed, as only 45 c.c. of the fluid was examined.

9. *Bile.*—No trace of proteid.

[1] The amount of precipitate used for this test was quite sufficient for the purpose.

10. *Blood.*—55 grammes of clotted blood from the heart was examined. This was extracted with water, and the extract examined by both methods. In neither case was the slightest trace of proteid obtained.

Consideration of results.—From an examination of these results it will be seen that in no organ or tissue could the presence of a proteid identical with that found by the same methods in the urine be demonstrated. In the case of the vertebræ and ends of the femur, however, a *proteid giving very similar reactions* was obtained. It will be noticed that the points wherein this differs most from the typical Bence-Jones proteid are the temperature at which it coagulates, and the fact that it does not clear up on boiling. It will also be noticed that after the addition of the merest trace of acetic acid the point of heat coagulation was the same as that in a similarly treated extract from urine, but whereas the urinary coagulum cleared up at 90° C., that of the marrow did not do so, even on boiling.

Recent work by K. Spiro,[1] Hammarsten,[2] and others shows, however, that not only does the exact point of heat coagulation vary considerably with the dilution and composition of the fluid, but also that re-solution of the coagulum depends to a very large extent on the composition of the fluid in which it is suspended.[3] In view of these facts it is impossible to draw any deductions as to the nature of the body from a consideration of the heat-coagulation point alone, and the mere fact that any proteid whatsoever should have been obtained after the processes to which the original extract was subjected shows in itself *that some unusual proteid existed in the tissues.*

Nor could such a proteid be obtained by employing exactly the same methods from normal red bone-marrow.

The neutralised opalescent solution obtained by the alcohol method gave a copious precipitate on weakly acidifying with acetic acid. This precipitate was soluble in excess of the acid. It was easily soluble in weak alkalies and gave the xantho-proteic and other reactions for proteids. This precipitate was not present in the dialysate obtained by the ammonium sulphate method. From its reactions

[1] Hoppe-Seyler's 'Zeit. f. phys. Chemie,' 1900, Bd. xxx, S. 182.

[2] Pflüger's 'Arch. f. d. ges. Physiologie,' 1878, Bd. xviii, S. 65.

[3] It was noticed, both in the case of the urine and of the vertebral marrow, that, on allowing the extract to stand for four weeks in a stoppered bottle, a sediment had settled down. This was filtered off, and the clear filtrate failed to give any reaction for proteids. The precipitate was insoluble in weak alkalies. The albumose-like body had evidently undergone a change on standing. There was unfortunately not sufficient material to re-investigate this fact.

it would appear to be either an alkali-albumen or a nucleo-proteid. To decide this question it was tested for phosphorus, with a negative result. It is probable, therefore, that a certain amount of alkali-albumen had been produced out of the alcohol coagula by boiling with dilute ammonia. After the separation of this by neutralisation and dialysis, a clear solution giving exactly the same reactions as the ammonium sulphate extracts was obtained.

The extract obtained from the red-currant-jelly-like marrow found in the shaft of the femur contained only the minutest trace of proteid.

The only other tissue from which a proteid-containing extract could be obtained was the kidney, and here only in the minutest trace. The pericardial fluid gave rather clearer reactions than the kidneys, a result in accordance with Ellinger's observations.

Conclusions regarding the Seat of Production of Bence-Jones Proteid.

The invariable, or almost invariable occurrence of bone-marrow disease in cases of Bence-Jones albumosuria would seem to point out the seat of production of this unusual proteid; but yet, when one considers the enormous quantities excreted daily—15 grammes in the above case—it is at first sight difficult to conceive how such a source can be possible. Magnus-Levy calculates that the whole mass of the diseased red marrow could not contain more than 100 grammes of proteid, and argues that, in his case [1] at least, where the daily excretion in the urine often attained 36 grms., its derivation from the bones was impossible. In support of this contention, he points out that in those cases where the total urinary nitrogen was estimated it was found that nearly 40 per cent. of this was excreted as Bence-Jones proteid. In a case investigated by Seegelken,[2] however, only about 10 per cent. of the total nitrogen was so excreted. From a consideration of these facts, Magnus-Levy supposes that the bone-marrow cannot be the seat of its production, but that it represents a non-assimilated digestive proteid. This want of assimilation he ascribes to the absence of some influence which the bone-marrow normally exercises on the metabolism of proteid, but which is wanting when the marrow is diseased.

In the above case, however, the results point to the bone-marrow as the seat of production, and the absence of any proteid in the

[1] Case No. 11 in the Summary.

[2] 'Deut. Arch. f. klin. Med.,' Bd. lviii, S. 276. (See Case No. 6 in the Summary.)

extract from nearly all the other tissues and organs would tend to disprove Magnus-Levy's theory, for were this correct we should expect to find at least some of the unusual proteid present in those organs (muscles, liver, etc.) where proteid metabolism is most active.[1]

The body was not found in the blood, and this was probably due to the fact that only a limited quantity was procurable for examination. Its presence in the kidneys was to be expected, since a certain amount of urine must still have been present in the tubules.

Summary of the Present Case.

The patient, a rather fat man, aged 50, complained of rheumatoid symptoms, commencing, so he thought, about the end of the year 1899. About February, 1900, he began to suffer from pains in his loins and stiffness in the small joints of his hands. Soon afterwards the upper part of his back began to bend, so that he always had a stooping attitude. Previously to this illness the patient had been strong, but as a young man had had gonorrhœa and a chancre on the penis. One of his sisters suffered from diabetes mellitus.

The urine of the patient was found to contain the Bence-Jones proteid. The daily amount of the urine was about 2000 c.c., and it contained about 7 per mille of the proteid as measured by Esbach's albuminimeter. By a more exact method (precipitation with alcohol, drying and weighing) Dr. R. Hutchison found that about 15 grammes of the proteid were excreted daily. The reactions of the proteid were the typical ones described by Bence-Jones, Kühne, Bradshaw, etc.

For some time the patient's condition remained fairly stationary, and at first, by the use of local hot baths, massage, etc., the power of bending his fingers was

[1] It is certainly difficult to conceive how so much proteid could be derived from so small a source, but still, when we take into account other metabolic processes in the body, *e. g.* the occurrence of 30 grammes of urea in the urine and of only two grammes in the whole body, the result does not seem so surprising.

improved. Afterwards, however, the general weakness, cachexia, and anæmia greatly progressed, and gummatous disease of the tongue and over one rib made its appearance. Examination of the blood showed great anæmia and slight leucocytosis. On January 25th the patient died after copious hæmorrhage from the intestines, which post-mortem examination showed to be due to chronic ulceration of the duodenum. The Bence-Jones albumosuria persisted to the last.

At the necropsy the bone-marrow of all the bones examined was found to be more or less affected by a diffuse sarcoma-like growth of rounded or polyhedral mononuclear cells—a form of "multiple myeloma" or "myelomatosis." There were no localised outgrowths projecting from the bones, such as have been noted in some cases of multiple myeloma, and no other parts of the body were invaded. In fact, as the neoplasm was strictly limited to the osseous system, no parts of it could be regarded as metastatic. The presence in the tumour-cells of certain granules and globules of various sizes constituted a striking histological feature in the present case.

Dr. R. Hutchison and Dr. J. J. R. Macleod made a careful chemical investigation of the bones, blood, and organs, but failed to find in any of these tissues and organs a body giving exactly the same reactions as those of the Bence-Jones proteid in the urine. From the vertebræ and ends of the femur, however, they obtained a proteid giving very similar reactions, differing somewhat in the temperature at which it coagulates and in not being re-dissolved on boiling. Moreover no proteid like that they detected could be derived, by employing the same methods, from normal red bone-marrow. They argue that in the present case the bone-marrow was probably the seat of production of the proteid excreted in the urine, and that this proteid is not a non-assimilated digestive proteid, as suggested by Magnus-Levy. Though the case was complicated with syphilitic gummata, chronic ulcera-

tion of the duodenum, and a generalised rheumatoid affection of the joints, it was a typical one of multiple myeloma with Bence-Jones proteid in the urine, the "myelopathic albumosuria" of Dr. T. R. Bradshaw, also called in Italy "Kahler's disease." When the diagnosis was first made it was probably the second case of the kind recognised during life in England, the first one being that of Dr. Bradshaw in 1898 (Case No. 10 in the Summary).

Remarks on Multiple Myeloma in General.

Multiple myeloma may be defined as a diffuse new growth primarily involving the bone-marrow, especially that of the vertebræ, ribs, and sternum,[1] and affecting males as or more often than females, and chiefly those past middle age. The disease nearly always remains limited to the osseous system, though by direct extension it may form localised outgrowths projecting from the bones. Owing to absorption of the hard osseous tissue the bones become softened or friable, and are easily broken. The vertebral column and sternum are sometimes much bent, and the spinal cord may be affected by pressure, due to the curvature of the spinal column or to new growth bulging into the spinal canal. Owing to the destruction of bone-marrow the formation of blood is impaired, and anæmia and progressive cachexia occur, doubtless in some cases favoured by the circulation of a toxic proteid. I cannot help drawing an analogy between the bone disease, myelomatosis (*i. e.* multiple myeloma), on the one hand, and the skin disease, mycosis fungoides, on the other. In both cases the ætiology, as well as the

[1] In the present case, however, and in some other cases (see Nos. 20 and 24 in the Summary), the bones of the limbs were likewise much affected. Doubtless if the whole skeleton had been examined, the long bones would have been found affected in some of the cases in which by the clinical symptoms the bone disease was supposed to be limited to the ribs, sternum, and vertebral column.

true nature of the new growth, is obscure. For both diseases an infection theory has been propounded, making the new growths allied to the class of infective granulomata; but at present the arguments in favour of any such infection theory are far from convincing. In myelomatosis there is a primary diffuse infiltration of the bone-marrow of a great part of the skeleton, followed in some cases by the formation of definite localised tumours growing from the bones; whilst mycosis fungoides usually commences as a diffuse infiltration of the skin (præmycotic stage), and the localised tumours, which give the disease its name, begin to sprout out later on. This analogy may perhaps turn out to be a very superficial one, but in the present uncertainty regarding both diseases it is worthy of mention. In one important point, indeed, the analogy is imperfect. The point is that, whilst mycosis fungoides seems to be a single definite disease (morbid entity), different kinds of neoplasm have apparently been included under the heading "multiple myeloma."

Multiple myeloma is a term which has been employed to include various diffuse new growths arising in the bone-marrow (*i. e.* myelogenic), and not giving rise to definitely metastatic growths in other tissues.[1] After post-mortem investigations various names have been employed according to the histological features (and individual interpretations by observers) of the neoplasms, and particularly of the cell-elements of which the tumours are formed. The tumours have been regarded as simple overgrowth of the cell-elements of the bone-marrow, or as myelogenic sarcoma, endothelioma, perithelioma, plasmoma, etc. In my first case[2] of "multiple myeloma" I supposed the tumour formation to be an example of "general lymphadenomatosis of bones." I have lately been able to re-examine the growth and get sections

[1] See later on in regard to the lymphatic glands becoming affected in some cases.

[2] "General Lymphadenomatosis of Bones, one form of 'Multiple Myeloma,'" 'Trans. Path. Soc.,' 1897, *loc. cit.*

stained by special methods. Following is a short abstract of the case:

The patient, E. P—, a man aged 61 years, was admitted to the German Hospital October 17th, 1896, complaining of various pains, resembling those often described in rheumatoid arthritis. His illness was apparently of comparatively recent onset. He was rather emaciated, and looked older than he really was—more like a man of 80 than of 61 years. He walked very stiffly and carefully with the aid of a stick. There was considerable kyphosis, and this seemed to be progressive. No organic disease could be found in the viscera, and the urine, according to the single note entered, was free from albumen. The blood was unfortunately not examined. Various medicines were tried, including glycerophosphates, iodide of iron, and arsenic, but they had no obvious effect. The patient had a fair appetite, and was free from fever; yet he seemed to get weaker and to complain more of the pains. The bilateral pains in the sides of the abdomen, which were usually worse when the patient stood up, and the increasing lumbo-dorsal kyphosis made one think of the possibility of malignant disease of the spinal column, of vertebral caries, or of spondylitis deformans. The whole spinal column was kept rigidly fixed in one position. In December pneumonia developed and led to the patient's death on January 18th, 1897.

The *necropsy* showed greyish consolidation of the bases of both lungs. The heart presented nothing unnatural. The stomach was abnormally dilated. The spleen was slightly enlarged and soft, and its capsule was thickened. The liver, by macroscopical and microscopical examination, appeared normal. The kidneys had undergone a moderate degree of interstitial fibrosis, and in the cortex of one of them calcareous granules (microscopic calculi) were present, some of which were in close relation to minute cystic adenomata.

All the ribs, the whole vertebral column, the clavicles, the sternum, and the bones of the calvarium were examined, and were all found to be the site of a very vascular pulpy neoplasm, growing from the interior outwards. The ribs were converted into delicate tubes formed of periosteum, with only a thin, imperfect shell of bone; they were all stuffed full of the new growth. The slightest pressure sufficed to break them in any part. Many "spontaneous" fractures had occurred during life, and had already been thoroughly united by callus. Here and there the osseous tissue had been completely absorbed, so that the new growth lay directly under the periosteum, and in some places the periosteum and bony shell had been bulged out by the tumour so as to form nodular enlargements on the

ribs. The clavicles were somewhat less affected than the ribs, sternum, and vertebral column. There was a certain amount of new growth in the diploë of the cranial bones. Specimens of the new growth from the vertebræ, ribs, and diploë of the skull were microscopically examined, and consisted of rather small mononuclear cells, with none, or scarcely any substance between them. Interspersed amongst the cells were small blood-vessels, with swollen-looking, almost hyaline walls.[1] Examination of spicules of bone taken from the growth seemed to show that the bone was being absorbed by the tumour formation without undergoing any preliminary process of softening (decalcification), such as is reported to occur in osteomalacia and in the absorption of the bone trabeculæ in the long bones in some cases of pernicious anæmia.[2]

I have not yet mentioned that behind the right clavicle some enlarged lymphatic glands were found, which the microscope showed to be the site of a similar (but less vascular) growth to that of the bone-marrow. No tumour was discovered in other lymphatic glands or elsewhere in the body.

Recent re-examination of old sections (stained by the ordinary methods) from the bone-marrow growth, and from the affected glands, has confirmed the view and made it practically certain that the growth in the glands is identical with that in the bones. The cells of which the growth consists resemble lymphocytes, except that very many of them have more protoplasm than ordinary small lymphocytes have. The larger cells are rounded, oval, or polyhedral, and the nucleus is often placed excentrically. Part of the sternum was fortunately preserved in glycerine and formalin in the Museum of the Royal College of Surgeons, and thus I have lately had an opportunity of examining sections of the sternal portion of the growth stained by Ehrlich's tri-acid and by Mann's eosin-methyl-blue combinations. These stains show that hardly any of the cells contain granules. In fact, only one or two coarsely granular eosinophile cells were seen in looking through the sections, and these were probably not tumour-cells. The tumour may, therefore, be said to consist of non-granular, lymphocyte-like cells. The majority of these cells have more protoplasm than ordinary small lymphocytes have. It must be remembered, however, that in lymphatic leucocythæmia the growths in the various organs may

[1] From recent examination of portions of the growth from the sternum, I think that some of these supposed vessels are really vesicles remaining from fat-cells.

[2] Cf. "On the Changes of the Bone-marrow in Pernicious Anæmia," by R. Muir, 'Journal of Pathology,' 1894, vol. ii, p. 363.

consist largely of cells which, though they are described as lymphocyte-like, have much more protoplasm than do the small lymphocytes of normal blood. Every intermediate form between the cells with much protoplasm and those with very little protoplasm can be found in the growths of lymphatic leucocythæmia; and so they can be in the myelogenic growth from the patient E. P—. Moreover in normal lymphatic glandular tissue many of the cells of the "germinating centres" have more protoplasm than the small lymphocytes further from these centres and in the circulating blood. I feel justified, therefore, in saying that in the case of E. P— the cells of the myelogenic growth were lymphocyte-like, if not actually of the lymphocyte kind. Dr. J. M. H. MacLeod has kindly examined the growth by special staining for plasma-cells, and thinks that the cells of which the growth is composed have a greater resemblance to lymphocytes than to the typical plasma-cells of the granulomata.[1]

Two types, if not more, of "multiple myeloma" are to be distinguished—(1) a growth, as in the patient J. T—, in which the bone-marrow only is involved; (2) a growth in which nearly all the cells resemble small or large lymphocytes, and are possibly derived from the non-granular predecessors of the myelocytes;[2] in this second type of "multiple myeloma" lymphatic glands as well as bone-marrow may probably be affected. The second type of multiple myeloma would include cases described as myelogenic lympho-sarcoma, myelogenic lymphadenoma, and myelogenic pseudo-leukæmia (using the German term "leukæmia" in the limited sense of "lympho-cythæmia"). Intermediate cases between these two types ("mixed forms") probably also occur (cf. remarks under Case No. 16 in the Summary at the end).

[1] I may add that in part of the growth in the sternum many of the tumour-cells have undergone some kind of a degenerative change, owing to which, by Mann's eosin-methyl-blue combination, the nucleus and the rest of the cell are deeply stained by the eosin.

[2] Cf. A. Pappenheim, 'Virchow's Archiv,' 1902, vol. clxix, p. 381. According to his views the *large lymphocyte* type of cell, which in the lymphatic glands gives rise to the ordinary small lymphocytes of the blood, in the bone-marrow gives rise to the myelocytes and thus indirectly to the polymorphonuclear leucocytes also.

If the views which I have suggested in this paper be correct, it follows that the *whole class of leukæmias and pseudo-leukæmias* (using the German terms for convenience) can be divided into at least the following six types, independently of intermediate forms:

(*a*) A new growth of lymphocyte-like cells originating in the bone-marrow and not overflowing into the circulating blood.—Myelogenic pseudo-leukæmia (using leukæmia in the sense of lympho-cythæmia), myelogenic lympho-sarcoma, lymphadenomatosis of bones, multiple myeloma (myelomatosis) of the lymphatic type.

(*b*) Similar to the preceding, but the lymphocyte-like cells overflow into the blood-stream.—Myelogenic lymphocythæmia. I do not know of any cases illustrating this type, excepting cases of "acute leukæmia." Those of A. Dennig[1] and C. H. Melland,[2] for instance, were examples of acute lympho-cythæmia in which post mortem practically no change was discovered in the leucocyte-forming tissues other than the bone-marrow.

(*c*) A new growth formed in large part of lymphocyte-like cells originating in the lymph-glands or lymphadenoid tissues generally, and not to any great extent overflowing into the circulating blood.—Lymphatic or splenic lymphadenoma or pseudo-leukæmia (using leukæmia in the sense of lympho-cythæmia), Hodgkin's disease. In the more chronic and fibrous varieties of this type the microscopic appearances differ, of course, considerably from those in acute cases.

(*d*) Similar to the preceding, but the lymphocyte-like cells invade the blood-stream.—Lymphatic or splenic lympho-cythæmia.

(*e*) A new growth, originating in the bone-marrow, of cells derived from the myelocytes, not invading the circulating blood.—Myelogenic pseudo-leukæmia (using leukæmia in the sense of myelogenic or spleno-medullary

[1] 'Muenchener medicinische Wochenschrift,' January 22nd, 1901, No. 4, p. 140.

[2] 'Medical Chronicle,' September, 1902, p. 372.

leucocythæmia). To cases of this type the term *multiple myeloma* (*myelomatosis*) might perhaps be limited.

(*f*) A new growth characterised by its myelocyte-like cells overflowing or being drawn out into the circulating blood, and by Bence-Jones albumosuria not occurring, as it sometimes does in the last type (*e*).—Myelogenic or spleno-medullary leukæmia (leucocythæmia).

According to this scheme one must regard the excess of white corpuscles in the blood in all kinds of leukæmia as due to an inroad of tumour-cells from a *hyperplasia-like* tumour-formation in the leucocyte-forming tissues of the body,[1] all forms of leucocytosis (including lymphocytosis) being merely expressions of some reaction in the tissues in question. A leucocytosis is therefore, strictly speaking, never an early stage of leukæmia (leucocythæmia); yet a true leucocytosis from any cause may perhaps sometimes be followed by true leukæmia, in so far as a reactive growth in leucocyte-forming tissues (of which reactive growth the leucocytosis is the expression) may be supposed to give a start to the kind of tumour-formation of which the leukæmia is the expression, just as chronic irritation of the skin sometimes acts as the exciting cause of epithelioma.

Remarks on Multiple Myeloma with Bence-Jones Proteid in the Urine.

I shall now, however, confine my remarks to the present case and similar cases in which multiple myeloma is associated with the presence of Bence-Jones proteid in the urine. Though their microscopic appearances may somewhat vary, the growths in this group of cases are allied to each other by one notable peculiarity—a metabolic one—namely, that they form or cause to be formed in the body a substance which is got rid of by the kidneys as Bence-Jones proteid. Some striking features in the present case deserve special consideration.

[1] Cf. Pappenheim's various writings, loc. cit., etc.

Special Features of the Present Case.

The articular disease.—It was the affection of the hands, amounting to a "pseudo-paralysis," that obliged the patient to give up work and seek the hospital. The history in this respect is important. He was a stout, middle-aged, sallow-looking man, suffering from tingling sensations in the tips of his fingers (a kind of "acro-paræsthesia") and inability to grasp objects. He could not close his hands, and any attempt to bend his fingers caused pain. The back of the hands had a puffy, swollen appearance, especially about the metacarpo-phalangeal joints, and the fingers were tremulous. There was some pigmentation of the skin, and the fleshy portions of the finger-tips were shrivelled. The shoulder-joints were also somewhat affected, and doubtless the wasting noticed in the muscles of the upper extremities could be accounted for by the articular affection. After death from other causes marked changes were found in the joints examined—namely, in the hip, shoulder, wrist, and fingers. There can be no doubt that the patient suffered from a form of rheumatoid or rheumatic[1] arthritis, and that most of the early symptoms which he complained of were due to the arthritic affection, not to the myelomatosis of bones.

Whether or not the tumour-formation in the bones had any causal connection with the articular disease must remain doubtful. That joint changes can be induced by the irritation set up by tumour-formation in the neighbouring bones is made probable by an observation of Mr. Jonathan Hutchinson.[2] His case was that of a young woman whose thigh was amputated for a tumour of the tibia, and in whose knee-joint changes were discovered such as occur in rheumatoid arthritis.

The articular symptoms in the present case may be

[1] The evidence of former endocarditis found in the heart suggests that at one time there was acute rheumatism.

[2] 'Med. Times and Gazette,' 1881; quoted in Fagge and Pye-Smith's 'Principles and Practice of Medicine,' vol. ii.

compared to those of a type of early rheumatoid arthritis, referred to by Dr. J. Kent Spender,[1] in which the commencement is by sudden weakness in the hands. The patient complains that the hands cannot "hold" and that the fingers are "going to be paralysed," and there may be paræsthesia described as "burning," "scalding," or "scraping," together with vaso-motor disturbance. In the present instance the "pseudo-paralysis" of the hands, though it was to some extent relieved by local treatment (hot baths, massage, etc.), was explained by the structural changes (synovial fringes, etc.) in the small joints, which were still present when the patient died from other causes. The articular affection was, however, certainly not limited to the hands, as the post-mortem examination showed, though it was the inability to use his fingers that roused the patient's attention and obliged him to give up work.

I should like in passing to draw attention to a characteristic feature in certain affections of the small joints of the upper extremities, to which I believe sufficient attention has not yet been paid—namely, the presence of tremor of the fingers. This tremulousness[2] of the fingers is very characteristic when associated with a puffy swelling of the back of the hand, with a certain amount of shrivelling of the finger-tips, with inability to flex the phalangeal and metacarpo-phalangeal joints, and consequently with loss of power to grasp objects. The tremors are best observed when the fingers are separated or when the patient is endeavouring to move either his fingers or his whole hand. Each finger trembles as a whole from the metacarpo-phalangeal articulation, and the movements constituting the tremor in each finger are not necessarily synchronous with those in the other fingers. The type is therefore rather that of alcoholic and of certain other toxic tremors.

[1] Allbutt's 'System of Medicine,' vol. iii, p. 81.

[2] Perhaps the word "tremulousness" suits the irregularity of the movements better than "tremor" does; but the latter is shorter, and is, I believe, generally used to include all movements which are quick, small, and frequent, even if not strictly rhythmical in character.

This tremor may be unilateral in cases of gonorrhœal rheumatism of the wrist and hand, in which disease it is apt to occur during the subacute or chronic stage associated with trophic changes in the fingers and muscular wasting,—that is, at a period when the disease often resembles chronic tuberculosis of the wrist-joint. In connection with the tremor the negative result from examination of the nervous system in the present case is perhaps worthy of remark, though it is what one would expect.

The syphilitic affection.—The gummatous disease of the tongue and rib makes it clear that the patient really had syphilis, although he could not remember having had a secondary eruption. Considering how apt tertiary syphilis is to affect the bones, it is just possible that in this case it may have acted as an exciting cause in regard to the tumour-formation (myelomatosis).[1] In a similar way the irritation of the osseous changes in osteitis deformans and chronic osteomalacia[2] may be supposed sometimes to excite the development of primary bone-

[1] It is worth mentioning that in the case described by Sir H. Weber in 1866 ('Trans. Path. Soc.,' 1867, vol. xviii, p. 206), which would probably now be regarded as one of multiple myeloma, the patient, a man forty years of age, had had syphilis fourteen to sixteen years before death, and had amyloid disease of the kidneys and spleen. The sternum, ribs, vertebral column, and cranium were affected by a growth which Hulke and Cayley, who reported on it, were inclined to regard as sarcomatous. The state of the urine is not alluded to. The alteration in shape of the sternum was so great that it caused pressure on the aorta with physical signs simulating aneurysm.

[2] The occasional occurrence of primary malignant tumours in the bones in cases of osteitis deformans has been recognised since Sir James Paget's original description of the disease in 1876 ('Med.-Chir. Trans.,' vol. lx). Dr. Wilhelm Schönenberger ('Virchow's Archiv,' 1901, vol. clxv, pp. 189—226) gives the case of a woman aged 33 in which the changes of osteomalacia apparently preceded the development of multiple sarcomata (multiple fractures had also occurred). He likewise speaks of solitary or multiple sarcomata often developing in the late stages of "osteomalacia chronica deformans hypertrophica." It may be asked, however, whether these late forms of osteomalacia (showing a kind of hypertrophic reaction with new bone-formation) are not identical with osteitis deformans except for their history.

tumours, and chronic malaria seems occasionally to have acted as an exciting cause in the development of leucocythæmia.[1] On the whole, however, it is more probable in the present case that the cachectic condition of the patient led to the outbreak of tertiary syphilis. For, in syphilitic subjects, fevers and other general debilitating conditions, and (locally) traumatisms, favour the onset of gummatous disease.

The duodenal ulceration.—There is no doubt that the severe intestinal hæmorrhage greatly accelerated death in the present case. This may partly account for the fact that in the patient in question the tumour had, at the time of death, caused less destruction of bony tissue than in certain other patients with multiple myeloma; but it must also be noted that the man was strongly built, and the outside of his bones may have been specially resistent. Most patients with multiple myeloma, as I pointed out in 1897,[2] die of pneumonia, but the fatal result of the hæmorrhage in the present case interfered with the ordinary course of events. The duodenal affection is probably to be classed with the duodenal ulcers associated with renal disease.[3] The excretion of an irritant substance by the intestinal mucous membrane possibly accounts not only for duodenal ulceration, but also for ulcerative colitis when occurring in cases of renal disease.

The Bence-Jones Proteid in the Urine of Multiple Myeloma Cases.

The reactions of the proteid in the urine have already been described in the report by Drs. Hutchison and Macleod. They conclude that in the present case the

[1] For instance, in the case of leucocythæmia with Menière's symptoms which I communicated in 1900 ('Med.-Chir. Trans.,' vol. lxxxiii, p. 185).

[2] 'Trans. Path. Soc.,' vol. xlviii, loc. cit.

[3] See "On Diseases of the Duodenum," by E. C. Perry and L. E. Shaw, 'Guy's Hospital Reports,' 1893, vol. l, pp. 194—196 and 250—255.

bone-marrow was probably the seat of production of the proteid in question, and that this proteid is not a non-assimilated digestive proteid, as suggested by Magnus-Levy.[1] As confirming their views, I will repeat that in my patient a considerable alteration of diet maintained during two days had no effect in altering the quantity of proteid excreted in the urine. Moreover Dr. Bradshaw, in his case, found that meals had little or no influence on the excretion of the proteid in the urine. He found that as much was excreted by night as by day,[2] when the patient was taking meals during the daytime only; and he considered the rate of excretion to be "pretty constant throughout the twenty-four hours."

It seems probable that when it is free in the blood the Bence-Jones proteid appears in the urine,[3] like hæmoglobin does whenever owing to various causes sudden unusual hæmolysis occurs. The fact, therefore, that the quantity excreted in the urine is little influenced by meals and by change of diet speaks strongly against the correctness of Magnus-Levy's views. It is possible that the cells of the new growth in the bone may produce digestive enzymes, by the action of which on the albuminous constituents of the blood-serum the Bence-Jones proteid is steadily and continually manufactured. Then from the circulating blood it would pass through the renal filter with the urine, like hæmoglobin, even in the absence of any kidney disease. As already mentioned, there may be some connection between the excretion of the proteid in the urine and the formation of granules and globules in the cells of the new growth in the present case.

[1] Loc. cit.

[2] See the tables at the end of Dr. Bradshaw's first paper ('Med.-Chir. Trans.,' 1898, vol. lxxxi, pp. 270, 271).

[3] Stokvis found that Bence-Jones proteid, when a not very concentrated solution was injected into the rectum of a dog, was excreted unchanged in the urine. I have to thank Sir Lauder Brunton for directing my attention to these little-known experiments of Stokvis, which were recorded in the 'Maandblad der sectie voor Natuurwetenschappen,' 1872, No. 6.

Diagnosis of Multiple Myeloma (Myelomatosis) with and without Bence-Jones Proteid in the Urine.

There is still much uncertainty as to the nature of multiple myeloma (Multiples Myelom), a term first employed by J. von Rustizky,[1] who regarded the growth as formed by a simple hypertrophy of bone-marrow. As already mentioned, however, the tumours from different cases do not all resemble each other in their histological features, though they possess certain characters in common. The growth is generally so diffuse in its distribution that it is impossible to determine that any one part represents a primary focus where the neoplasm may be supposed to have commenced. It does not invade other tissues by metastasis through the blood-channels like sarcoma does, though in some cases the lymphatic glands have been involved (cf. Case 3 in the Summary at the end).

Owing to the softening and fragility of bones, the pains, and the progressive kyphosis caused by the disease, the diagnosis is firstly from—

(*a*) *Osteomalacia.*

(*b*) *Muscular rheumatism, lumbago, sciatica, etc.*

(*c*) *Spondylitis deformans.*

(*d*) *Caries of the spinal column.*

(*e*) *Invasion of the vertebral column and other bones by secondary malignant tumours.*

Owing to the progressive anæmia and cachexia, one may think of—

(*f*) *Pernicious anæmia or other diseases associated with progressive cachexia.*

Owing to the possibility of confusing Bence-Jones proteid in the urine with albumen, the cases of multiple myeloma in which this body is present in the urine (*i. e.*

[1] "Multiples Myelom," 'Deutsche Zeitschrift für Chirurgie,' Leipzig, 1873, vol. iii, p. 162.

the cases of "myelopathic albumosuria" of Bradshaw, "Kahler's disease") may be at first mistaken for—

(*g*) *Nephritis.*

(*a*) *Osteomalacia.*—From the typical osteomalacia of women multiple myeloma differs in the following respects. The former attacks women during the child-bearing period of life. It affects chiefly the bones of the pelvis and lower extremities. It gives rise to great deformity by the bending of the bones, but more rarely to "spontaneous" fractures. Multiple myeloma attacks men as often as women, or more often, and chiefly those in the second half of life. Clinically, it appears specially to affect the vertebral column, ribs, and sternum, though the bones of the extremities have certainly been involved in some cases, as they were in my present case. It is likely to cause fractures of the ribs and deformity by bending of the vertebral column and sternum; in one case (Case No. 20 in the Summary) "spontaneous" fracture of one femur occurred, and in another (Case No. 24 in the Summary) "spontaneous" fractures of both femora are recorded; yet it does not give rise to the characteristic deformities of osteomalacia, resulting from yielding of the pelvis and bending of the bones of the lower extremities. It is possible, however, that there may be true cases of osteomalacia in males and in elder females, in which the bones of the vertebral column and trunk are specially affected.

(*b*) *Muscular rheumatism, lumbago, sciatica, etc.*—Several cases of multiple myeloma have, at least during part of the disease, been given such headings. The occurrence of markedly bilateral thoracic, abdominal, or lumbago-like pains may first direct attention to the possibility of disease of the spinal column. In my first case of multiple myeloma,[1] pain on both sides of the abdomen, together with the presence of an increasing kyphosis, pointed to grave disease of the spinal vertebræ. Some-

[1] 'Trans. Path. Soc.,' loc. cit.

times examination of the bones by Röntgen's rays may prove of service (*vide* Case No. 13 in the Summary at the end). If grave rheumatoid or rheumatic arthritis is a complication, as in my present case, it obviously becomes difficult to distinguish pains and paræsthesiæ due to the arthritis from those due to the multiple myeloma.

(*c*) *Spondylitis deformans.*—This affection of the vertebral columns may produce a similar kyphosis to that which in several cases has been caused by multiple myeloma. When, however, the kyphosis is due to spondylitis deformans,[1] the spinal rigidity in the cervical region is probably more pronounced than in cases of multiple myeloma, whilst the patient is likely to be less anæmic and cachectic. For comparison with my illustration of the present case of multiple myeloma (Plate I), I am able, by the kindness of my colleague, Dr. zum Busch, to give the illustration of a spondylitis deformans patient (the so-called "spondylose rhizomélique" type of Pierre Marie, at a relatively early stage of the disease) (Plate II) under his care, whom I also had formerly seen in the out-patient department. The portrait of Dr. Bradshaw's patient, illustrating his paper before the Medical and Chirurgical Society of London in April, 1898 ('Transactions,' 1898, vol. lxxxi, Plate VII), should likewise be consulted for comparison (reproduced here by permission, Plate III).

(*d*) *Caries of the spinal column.*—The progressive bend-

[1] Cases in which the vertebral column only is affected (von Bechterew's type) may be distinguished from those in which the extremities, especially the hip-joints, are likewise affected (Strümpell's type, Pierre Marie's "spondylose rhizomélique"). Such cases of chronic ossifying arthritis may progress to universal bony ankylosis. (See the summary of cases by Dr. Joseph Griffiths in the 'Journal of Pathology and Bacteriology,' December, 1896, and March and June, 1897. Much has been written on the subject during recent years in France and Germany.) Of course, when ankylosis of the joints of the extremities has occurred, a case could hardly be mistaken for one of multiple myeloma, but even at the commencement of the disease such a mistake is very unlikely to be made.

ing of the vertebral column seen in multiple myeloma might be confused with tuberculous caries,—that is, with those rather rare cases occurring in middle or old age and giving rise to progressive curvature. On the other hand, the curvature due to myeloma is somewhat less likely to be distinctly "angular" than that due to tuberculosis, and in the latter disease the ribs are not likely to be in any way affected simultaneously with the spinal column. The sternum has sometimes become excessively bent in multiple myeloma. The presence of tuberculosis in the lungs might help to clear up the diagnosis.

(*e*) *Invasion of the vertebral column and other bones by secondary malignant tumours.*—Secondary localised malignant tumours may give rise to a progressive curvature of the vertebral column. The vertebral column and ribs may likewise be diffusely infiltrated by metastatic carcinoma, but all such metastatic growths are more likely to cause distinct swellings[1] or give rise to local signs of their presence. Evidence as to a primary malignant growth existing or having been removed from some other part of the body would facilitate the diagnosis, and in localised tumours, as well as in tuberculous caries, help might be obtainable from the Röntgen rays.

(*f*) *Pernicious anæmia, etc.*—Anæmia and progressive wasting and feebleness may be marked features of myelomatosis, at all events in the later stages, when the blood-forming functions of the bone-marrow are greatly impaired by the diffuse tumour-formation. The pains and other signs of bone disease, such as progressive kyphosis, when these are well marked, will help to distinguish cases of multiple myeloma from pernicious anæmia and forms of progressive cachexia dependent on visceral cancer, etc.

(*g*) *Nephritis.*—The Bence-Jones proteid when present in the urine may be confused with albumen, and the case

[1] In some cases, however, of multiple myeloma, with or without Bence-Jones proteid in the urine, localised tumours connected with the bones could be seen or felt during life. (See Cases 14, 19, 27, and 33 in the Summary at the end.)

may be regarded as one of nephritis. This is especially likely to occur if the urine on the first occasion is examined very hurriedly (for example, by heating it without boiling it, or by merely adding picric acid or nitric acid in the cold), and, owing to the copious precipitate of supposed ordinary albumen, it is subsequently examined every day by Esbach's tube. This actually occurred in the present case,[1] where the general "puffy" look of the patient seemed to correspond to the finding of albuminuria. Moreover in this case, as in some other cases, hyaline casts were found in the urine.[2] Afterwards the testing of the urine by the ordinary methods, instead of by Esbach's solution, led to the detection of the special proteid it contained.

I need not repeat what has already been said in regard to the tests to be employed for distinguishing Bence-Jones proteid in the urine from albumen and from certain albumoses.[3] In the albumosuria occasionally met with in cases of intestinal ulceration and febrile disorders, the quantity of proteid in the urine is generally far less than in Bence-Jones albumosuria. In such a case as that recorded by Dr. R. Hutchison,[4] where the proteid, though precipitated at as low a temperature as 58° C., was not, even partially, re-dissolved on heating to the boiling-point, the chances of wrongly regarding the precipitate as

[1] The remarkable *constancy in the amount* and the *large quantity* of the proteid in the urine ought perhaps to have caused some surprise.

[2] The necropsy, it should be remembered, showed the presence of actual interstitial fibrotic changes in the kidneys. In Senator's case (Case No. 7 in the Summary) casts and albumen were present in the urine, and the kidneys were found to be somewhat diseased at the post-mortem examination. In d'Allocco's case (No. 15) there was likewise nephritis; in Ellinger's (No. 9) the urine contained a few hyaline casts; and in Conti's (No. 27) during the last weeks of life the urine contained albumen and hyaline and granular casts.

[3] I do not think that Dr. L. N. Boston's caustic soda and lead acetate test ("A Rapid Reaction for Bence-Jones Albumose," 'American Journ. Med. Sci.,' October, 1902, p. 567) is likely to be of much service in this connection.

[4] Case No. 30 in the Summary of cases at the end.

one of ordinary urinary albumen must be still greater than they were in the present case, where the greater part of the precipitate re-dissolved on boiling the urine.

I now come to the *diagnostic value of finding Bence-Jones proteid in the urine*. From a study of cases the following conclusions must be arrived at:—(1) Undoubtedly a considerable number of cases of multiple myeloma have occurred in which the Bence-Jones proteid has not been detected. In some of them the urine may have been examined at a stage of the disease prior to the commencement of the "Bence-Jones albumosuria."[1] In other cases the urine may possibly have been insufficiently examined. Still there remain sufficient cases to enable one to affirm with almost absolute certainty that "multiple myeloma" may occur without giving rise to the presence of Bence-Jones proteid in the urine. It must be remembered, however, that different types of tumour have been included under the heading "multiple myeloma," but I will not repeat here the conclusions which I have already mentioned in an earlier part of the present paper. (2) Metastatic tumours affecting the skeleton, however extensively the bone-marrow be infiltrated, have never yet been known to cause "Bence-Jones albumosuria." (3) The presence of Bence-Jones proteid in the urine is almost invariably of fatal significance, and nearly always, if not always, indicates that the patient is suffering from "multiple myeloma." (4) One or two published cases in which Bence-Jones proteid was present in the urine seem, however, to have been exceptions to the rule, in that they were supposed not to be instances of multiple myeloma. Moreover the experiments of Dr. G. Zuelzer,[2] should they be confirmed,

[1] In the case of Stokvis and Kühne (Case No. 2 in the Summary), the Bence-Jones proteid is said to have appeared late in the disease, and could not be found three months before the patient's death. Conti says that during the last weeks of life in his case (No. 27 in the Summary) the urine contained albumen but no Bence-Jones proteid.

[2] "Ueber experimentelle Bence-Jones'sche Albumosurie," 'Berliner klinische Wochenschrift,' 1900, No. 40, p. 894.

would make the existence of such exceptions more probable. He rendered a dog anæmic by giving it pyrodin by the mouth. On the eighth day from the commencement of the experiment, a substance was detected in the urine giving the typical reactions for Bence-Jones proteid, and no albumen was present. The pure Bence-Jones albumosuria lasted four days, and then albuminuria occurred and the amount of the Bence-Jones proteid diminished. It would be interesting to know what changes occurred in the bone-marrow of this animal.

Taking all the data that I can obtain into consideration, it seems to me quite possible (1) that Bence-Jones albumosuria is always the result of disease of the bone-marrow; (2) that it is due to an abnormal metabolic or degenerative process in the myelocytes or in tumour-cells derived from the myelocytes or their predecessors; (3) that the reason why it is generally, though not always,[1] associated with myelogenic tumour formation is that the tumour-cells derived from bone-marrow cells, however much they may morphologically resemble true bone-marrow cells, are more prone to abnormality (including unusual degenerative changes) than real myelocytes are; (4) that non-myelogenic tumour-cells are not affected in the same way, and therefore metastatic tumours in the bone-marrow do not give rise to Bence-Jones albumosuria.

In further evidence of the correctness of these conclusions, I shall now give a very short summary of all the reported cases in which Bence-Jones proteid has been detected in the urine,[2] whether the presence of bone

[1] An analogy between Bence-Jones albumosuria and melanuria may be made. The presence of melanin and melanogen in the urine is best known in cases of melanotic tumour, but has been noted likewise in wasting diseases. Melanotic tumours, however, are not always associated with the excretion of melanin or melanogen in the urine. Yet, as Dr. A. E. Garrod points out ('St. Bart.'s Hosp. Rep.,' vol. xxxviii, p. 25), melanuria has been undervalued for diagnostic purposes because other conditions in which the urine blackens on exposure to air have been confounded with true melanuria.

[2] In preparing the list I am indebted to the summaries given in

disease was verified or not. I shall also refer to some doubtful cases, in which the reactions of the proteid in the urine were not quite characteristic for Bence-Jones proteid, and shall mention certain supposed cases obviously incorrectly included in previous summaries on the subject. For full details, however, the original papers, to which references are given under each case, must be consulted. Amongst doubtful cases are those, such as that reported by R. Hutchison (Case No. 30), in which, though a copious precipitate occurs on slightly heating the urine, yet this precipitate is not to any extent dissolved by further heating. In this connection it must be remembered that the experiments of Hammarsten,[1] K. Spiro,[2] Magnus-Levy,[3] and others in regard to various proteids, show that the point of heat coagulation varies with the dilution and composition of the fluid, and the resolution of the coagulum depends likewise to a great extent on the composition of the fluid in which it is suspended. Amongst cases which should not be included in the Summary are those of albumosuria (other than "Bence-Jones albumosuria") in which no precipitate occurs on merely heating

various previous articles on the subject, particularly to that of Dr. C. E. Simon (*vide* Case No. 20). I shall not here refer to the cases of "multiple myeloma without albumosuria," several of which are quoted in my paper in vol. xlviii of the 'Transactions of the Pathological Society of London' (loc. cit.). On the whole subject of multiple myeloma, the important writings of F. W. Zahn ('Dent. Zeitschr. f. Chirurgie,' 1885, vol. xxii, p. 1), Hammer ('Virchow's Arch.,' vol. cxxxvii, p. 280), Markwald ('Virchow's Arch.,' vol. cxli, p. 128), R. Paltauf ('Ergebnisse der allg. Pathologie,' edited by Lubarsch and Ostertag, 1896, vol. i, pp. 676—679), K. Winkler ('Virchow's Arch.,' vol. clxi, p. 252), E. Wieland ('Virchow's Arch.,' vol. clxvi, p. 103), and M. Borst ('Die Lehre von den Geschwülsten,' 1902, vol. i, pp. 492—494) may be consulted. I have not studied the long paper by Dr. F. Harbitz on multiple primary tumours of bones (in the 'Norsk Magazin for Lægevidenskaben,' Christiania, 1903, Nos. 1 and 2), but in none of Harbitz's cases was Bence-Jones proteid detected in the urine.

[1] Loc. cit.

[2] Loc. cit.

[3] Loc. cit.

the urine (presumably acid in reaction), but in which the addition of nitric acid to the cold urine gives rise to a precipitate, which dissolves on heating and reappears on cooling.[1]

Summary of Cases.

No. 1. *The case of Watson, Macintyre, and Bence-Jones, of London.*—(H. Bence-Jones, "On a New Substance occurring in the Urine of a Patient with Mollities Ossium," 'Phil. Trans. Royal Society, London,' London, 1848, Part i, p. 55. W. Macintyre, "Case of Mollities and Fragilitas Ossium," 'Med.-Chir. Trans.,' London, 1850, vol. xxxiii, p. 211. J. Dalrymple, "On the Microscopical Character of Mollities Ossium," 'Dublin Quarterly Journ. Med. Sci.,' 1846, vol. ii, p. 85.)

The patient was a man aged 45, a patient of Dr. W. Macintyre and Sir Thomas Watson. His pains commenced after a strain in September, 1844. The proteid was present in the urine when a specimen was sent to Bence-Jones in November, 1845. Death occurred in

[1] A typical example of this is recorded by Hougounenq ('Lyon Médical,' vol. xcvi. Jan. 20th, 1901). See also E. Vidal's case ('Comptes rendus de la Société de Biologie,' October 29th, 1898, p. 991) in a woman, aged 24, suffering from tuberculous disease of the right shoulder. Dr. J. A. Blair's "Case of Albumosuria" ('Brit. Med. Journal,' September 14th, 1901, p. 713) is doubtless of the same kind. He states that the urine "gave no perceptible precipitate on simple heating without acid," but that on adding nitric acid to the cold urine a precipitate occurred which was dissolved on heating and reappeared on cooling. This kind of albumosuria is doubtless much less rare than the "Bence-Jones albumosuria," and is probably sometimes altogether overlooked owing to the fact that the boiling test for albumen is more often employed than the nitric acid (cold) test. It must be remembered, however, that in true Bence-Jones albumosuria the urine, if alkaline, should likewise not be expected to give any precipitate on heating until it has been rendered slightly acid, *e.g.* by the addition of acetic acid. The case described by Dr. Ter-Grigoriantz (Hoppe-Seyler's 'Zeit. f. Phys. Chemie,' Strassburg, vol. vi, p. 537) was certainly not an example of Bence-Jones albumosuria. He specially stated that no precipitate occurred on boiling the urine with or without the addition of acetic acid.

January, 1846. The condition of the bones at the necropsy was regarded as a kind of osteomalacia, but Dalrymple, who made a microscopical examination of two vertebræ and a rib, found that the process somewhat resembled malignant disease. Kahler was the first to suggest that the bone disease in this case was really, as in his own case, multiple myeloma.

No. 2. *The case of Doornik, Stokvis, and Kühne.*—(W. Kühne, "Ueber Hemialbumose im Harne," 'Zeitschrift für Biologie,' 1883, vol. xix, p. 209.)

The patient was a man aged 40, under the care of Dr. Merkus Doornik, of Amsterdam. He fell ill November, 1868, and died August, 1869, but it was not till many years later that notes of the case and an account of the characters of the urine were reported by Kühne. There were remarkable nervous symptoms, and the clinical diagnosis was acute osteomalacia of the spinal column with compression of the spinal cord; no post-mortem examination, however, was made. The Bence-Jones proteid in the urine of this case appeared late in the disease, and was not present during the last three months of the patient's life.

No. 3. *The case of Kahler and Huppert.*—(O. Kahler, "Zur Symptomatologie des Multiplen Myeloms: Beobachtung von Albumosurie," 'Prager medicinische Wochenschrift,' 1889, vol. xiv, p. 33. H. Huppert, "Ein Fall von Albumosurie," *ibid.*, p. 35.)

The patient was a medical man (Dr. Loos) aged 46, when the disease first showed itself in July, 1879. He suffered from severe pains, progressive kyphosis, and became deaf; the duration of the illness was eight years, therefore much longer than in the other cases yet known. The Bence-Jones proteid was present in the urine during the last six years. He died in August, 1887. From the post-mortem examination Kahler identified the bone disease with the "multiple myeloma" of von Rustizky

and Zahn, and suggested that Case No. 1 and Case No. 2 were likewise of the same nature. Though the clinical diagnosis had been osteomalacia, Kahler pointed out that in future the presence of the Bence-Jones proteid in the urine might help to distinguish cases of multiple myeloma from osteomalacia. It is owing to the light thrown on the subject by Kahler's communication that Bozzolo and certain subsequent Italian writers have named this form of disease "Malattia di Kahler." In Kahler's case the spleen was enlarged and the inguinal lymphatic glands on both sides were affected, and in connection with my recent case it is worth mentioning that the free edge of the mitral valve of the heart was found thickened.

No. 4. *The case of Stokvis, Ribbink, and Zeehuisen.*—(B. I. Stokvis, 'Nederl. Tijdschrift voor Geneesk.,' 1891, vol. ii, p. 36. H. C. G. Ribbink's 'Dissertation,' Amsterdam, 1892. H. Zeehuisen, 'Nederl. Tijdschrift voor Geneesk.,' 1893, vol. i, p. 829.[1] See also abstracts in 'Maly's Jahresbericht für Thier-Chem.,' vol. xxi, p. 412; vol. xxii, p. 525; vol. xxiii, p. 577.)

The patient was a man aged 39. During life there was Bence-Jones proteid in the urine, and this body was detected likewise in the fæces. After death a diffuse change in the bones was found, which was regarded as "osteo-sarcomatosis." There were likewise tumours of the serous membranes and of other parts of the body, but whether in any way connected with the bone disease is uncertain. "Calcareous metastases" were observed in the kidneys, such as Virchow has drawn attention to as sometimes occurring in cases of malignant tumours of bones.

No. 5. *The case of Raschkes.*—(A. Raschkes, "Ein Fall von seniler Osteomalacie mit Albumosurie," 'Prager

[1] There have been several articles on Bence-Jones albumosuria in Dutch journals. The literature of the subject was summed up by Tanja in 'Geneesk. Bladen,' 1901, No. xi. *Vide* also Case No. 26.

med. Wochenschrift,' December 20th, 1894, No. 51, p. 649.)

The patient was a woman aged 65, with great tenderness of all the bones to percussion, especially over the sternum, ribs, lumbar vertebræ, and hips. After a few weeks in the hospital she died of pneumonia. At the necropsy the diagnosis of the bone disease was "senile osteomalacia of the thorax" and "senile osteoporosis of humerus and femur," but in the light of recent cases it is probable that the case should be regarded as one of multiple myeloma. The urine contained albumen as well as Bence-Jones proteid, and the presence of chronic interstitial nephritis as a complication was confirmed by the post-mortem finding.

No. 6. *The case of Professor Stintzing, of Jena.*—(Seegelken, "Ueber Multiples Myelom und Stoffwechsel Untersuchungen bei derselben," 'Deut. Archiv für klin. Med.,' 1897, vol. lviii, p. 276. M. Matthes, "Ueber Eiweisskörper im Urine bei Osteomalacie," 'Verhandl. des XIV Congresses für innere Medicin,' 1896, p. 476. R. Neumeister, 'Lehrbuch der physiol. Chemie,' 1897, second edition, p. 804.)

The patient was a man aged 61, supposed to have osteomalacia, admitted to Stintzing's Clinic in September, 1895. The urine was studied by Matthes in Neumeister's laboratory. Death occurred in July, 1896. Seegelken termed the new growth which was found in the bones at the necropsy "chondrosarcoma." It may be noted with reference to the case described in the present paper that Stintzing's patient had suffered from articular "rheumatism" eight years before his fatal illness.

No. 7. *Senator's case.*—(H. Rosin, "Ueber einen eigenartigen Eiweisskörper in Harne und seine diagnostische Bedeutung," 'Berliner klin. Wochenschr.,' 1897, p. 1044. H. Senator, "Asthenische Lähmung, Albumosurie, und multiple Myelome," 'Berliner klin. Wochenschr.,' 1899,

p. 161. The urine has likewise been studied in Süssmann's 'Dissertation,' Leipzig, 1897.)

The patient, a woman aged 36, was first seen in February, 1897, and died in April of the same year. The case was complicated by a renal affection, and by a remarkable nervous affection regarded by Senator as asthenic bulbar paralysis (myasthenia gravis).

No. 8. *Bozzolo's case.*—(Camillo Bozzolo, "Sulla Malattia di Kahler," in the 'Transactions of the Eighth Medical Congress,' Naples, October, 1897; and in 'La Clinica Medica Italiana,' Milan, January, 1898, p. 1. Referred to also in 'Centralblatt für die med. Wissenschaft,' 1898, vol. xxxvi, p. 572.)

The patient was a native of Como, aged 42, the proprietor of an hotel in London, where he had suffered from pain in one loin and was reported to have albuminuria. Amongst the symptoms mentioned are pains in the vertebral column and ribs, curvature of the spinal column, and signs of pressure on the spinal cord (increased knee-jerks, etc.). His illness had probably lasted two years at least before Bozzolo saw him at Turin, where the examination of the urine by Bozzolo's assistant, Belfanti, showed that the case was not one of ordinary albuminuria. On heating the urine a precipitate commenced to form at about 45° C., and continued to increase till the temperature of 55° C. was reached, but dissolved up again on boiling. No necropsy is recorded.

No. 9. *The case of Lichtheim and Ellinger.*—(A. Ellinger, "Das Vorkommen des Bence-Jones'schen Körpers im Harn bei Tumoren des Knochenmarkes und seine diagnostische Bedeutung," 'Deut. Archiv für klin. Medicin,' 1899, vol. lxii, p. 255.)

The patient was a man aged 45, who was admitted to the Königsberg Clinic in October, 1897, and died in December of the same year. This case was complicated by jaundice and considerable fever. The urine, besides

the Bence-Jones proteid, contained a trace of albumen and a few hyaline casts. The spinal cord showed degenerative changes in the posterior columns. The changes found in the bones at the necropsy were regarded as diffuse lymphoid infiltration together with multiple lymphomatous tumours. After death the presence of Bence-Jones proteid was thought to have been proved in a piece of rib, and in some of the blood and ascitic fluid.

No. 10. *Bradshaw's case.*—(T. R. Bradshaw, "A Case of Albumosuria in which the Albumose was spontaneously precipitated," 'Med.-Chir. Trans.,' London, 1898, vol. lxxxi, p. 259. Bradshaw and Warrington, "The Morbid Anatomy and Pathology of Dr. Bradshaw's Case of Myelopathic Albumosuria," ibid., 1899, vol. lxxxii, p. 251. Bradshaw, 'Trans. Path. Soc.,' London, 1900, vol. li, p. 140. Bradshaw, "Myelopathic Albumosuria," 'Brit. Med. Journ.,' November 3rd, 1900, p. 1304. Bradshaw, "Myelopathic Albumosuria," 'Lancet,' October 4th, 1902, p. 929.)

A man aged 70 noticed in 1896 that his urine was sometimes "milky." In 1897 Dr. Bradshaw found that Bence-Jones proteid was constantly present in the patient's urine, and regarded the occasional milkiness as due to spontaneous precipitation of this proteid. The nature of the bone affection was therefore diagnosed during life, and this diagnosis was confirmed by an incomplete post-mortem examination after the patient's death in August, 1898. The kidneys showed a certain amount of interstitial fibrosis.

No. 11. *Case of Naunyn and Magnus-Levy.*—(Naunyn, "Ein Fall von Albumosurie," 'Deut. med. Wochenschrift,' 1898, Vereins-Beilage, p. 217. A. Magnus-Levy, "Ueber den Bence-Jones'schen Eiweisskörper," Hoppe-Seyler's 'Zeitschrift für phys. Chemie,' 1900, vol. xxx, p. 200.)

No necropsy was made. In this case, according to Naunyn, a spontaneous precipitation of Bence-Jones pro-

teid occurred in the urine on standing. Magnus-Levy, who carefully studied the urine, found that the daily excretion of the proteid in question often reached 36 grammes.

No. 12. *The first case of Dr. Fitz.*—(R. H. Fitz, "The Significance of Albumosuria in Medical Practice," 'American Journ. Med. Sci.,' 1898, vol. cxvi, p. 30.)

The patient, a woman aged 53, was first seen in November, 1895. The clinical diagnosis was myxœdema, and she died in April, 1896, whilst under treatment with thyroid extract. The urine was examined by Dr. E. S. Wood, but owing to there being no post-mortem examination, myelomatous bone disease cannot be excluded.

No. 13. *The second case of Dr. Fitz.*—(R. H. Fitz, loc. cit., p. 42. J. H. Wright, "A Case of Multiple Myeloma," 'Johns Hopkins Hospital Reports,' 1900, vol. ix, p. 359; also 'Journ. of the Boston Society of Med. Sci.,' 1900, vol. iv, p. 195.)

The urine was examined by Dr. E. S. Wood. The whole case and necropsy are recorded by Wright. The patient, at first under the charge of Dr. F. C. Shattuck, was a man aged 54, admitted to the Massachusetts General Hospital in February, 1898, where he died in July of the same year. In this case there were nervous symptoms, including diplopia, and some incontinence of urine. A fairly good history of syphilis was obtained. The Röntgen rays are stated to have been of great service in facilitating the recognition of the bone lesions.

No. 14. *The case of Buchschtab and Schaposchnikow.*—(L. Buchschtab and B. Schaposchnikow, "Diffuses Myelom der Rumpfknochen mit einer Typischen Albumosurie," abstract in German in 'St. Petersburger med. Wochenschrift,' 1899, from 'Russ. Arch. Pat., Klin. Med., Bact.,' vol. vii; also abstract in 'Centralblatt für allg. Pathologie,' 1899, vol. x, p. 589.)

The patient was a man aged 42, in the Israelitish Hospital at Odessa. The diagnosis of myelomatosis was made during life owing to the finding of Bence-Jones proteid in the urine. It was confirmed by the necropsy. In this case the symptoms of a "compression-myelitis" developed owing to tumours projecting into the spinal canal; swellings appeared on the ribs, and there was a large growth connected with the right iliac bone.

No. 15. *D'Allocco's case.*—(D'Allocco, "Sulla Malattia di Kahler," at the tenth Medical Congress, Rome, October, 1899, 'Arch. Ital. di Medicina Interna,' 1900, vol. iii, fasc. Nos. 1 and 2; referred to also by U. Flora in his article, "Sulla Malattia di Kahler," 'Rivista Critica di Clinica Medica,' Florence, 1900, Nos. 46 and 47.)

A man aged 44 commenced to suffer from a painful and deforming bone disease after a fall on his chest. There was constant Bence-Jones albumosuria, and death occurred in five months. Diffuse myelogenic sarcoma was the post-mortem anatomical diagnosis of the bone disease. Chronic nephritis was likewise diagnosed. In this case a spontaneous precipitate (supposed to be of Bence-Jones proteid) was noted in the urine. Tube-casts were also found, and the necropsy confirmed the existence of chronic nephritis as a complication. D'Allocco thinks that he demonstrated the presence of the Bence-Jones proteid in the patient's blood.

No. 16. *The case of Lichtheim and Askanazy.*—(S. Askanazy, "Ueber die diagnostische Bedeutung der Ausscheidung des Bence-Jones'schen Körpers durch den Harne," 'Dent. Archiv für klin. Medicin,' 1900, vol. lxviii, p. 34.)

The patient was a man aged 51, in Professor Lichtheim's Clinic at Königsberg. The amount of Bence-Jones proteid in the urine was only ½ to 1¼ per mille. Askanazy apparently succeeded in extracting a proteid identical with that in the urine from a portion of the

patient's bone-marrow obtained at the necropsy. The man certainly had lymphatic leucocythæmia, and Askanazy thinks that the bone disease was only part of the leucocythæmia. Possibly, however, the disease may have been a "mixed" form of multiple myeloma; that is to say, it may have been an example of the association of the two types of multiple myeloma to which I have previously referred—namely, a "lymphatic" type leading, in this instance, to lymphatic leucocythæmia,[1] and a type similar to that of my second case (patient J. T—), giving rise to Bence-Jones albumosuria. The latter form of myelogenic growth may have been still in an early stage of development, and may have escaped notice amidst the "lymphatic" growth at the post-mortem examination. This might likewise account for the relatively small amount of Bence-Jones proteid in the patient's urine.

No. 17. *Latzko and Sternberg's case.*—(M. Sternberg, in "Vegetationsstörungen und Systemerkrankungen der Knochen," Nothnagel's 'Spec. Path. u. Therapie,' 1899, vol. vii, part ii, division 2, p. 57.)

The patient was a woman aged 56, whom Sternberg saw with Dr. W. Latzko in November, 1897. She had been ill two years with pains in the bones, etc. Bence-Jones proteid in great quantity was found in the urine by Dr. E. Freund. Death occurred several months later, but no post-mortem examination could be made.

No. 18. *Barr's case.*—(J. Barr, "Case of Myelopathic Albumosuria," 'Liverpool Med.-Chir. Journal,' March, 1901, p. 23.)

The patient was a man aged 53. There were pains in

[1] A. Pappenheim has endeavoured to explain the fact of lymphatic leukæmia occasionally supervening on pseudo-leukæmia in 'Virchow's Archiv,' 1901, vol. clxvi, p. 473. See also the elaborate summary of his views regarding the relations of lymphocytes to plasma-cells, etc. ("Weitere kritische Ausführungen zum gegenwärtigen Stand der Plasmazellen Frage"), in 'Virchow's Arch.,' 1902, vol. clxix, pp. 372—428.

the spinal column, a swelling in the manubrium sterni, etc. The bone disease seemed to be of progressive character. Barr found the quantity of urine usually between forty and sixty ounces daily, and it rarely contained less than twelve per mille of the Bence-Jones proteid. I understand that no post-mortem examination was made. In connection with my own recent case it is interesting to note that Dr. Barr's patient presented undoubted signs of cardiac valvular disease.

No. 19. *The case of a French physician.* — (T. R. Bradshaw, "On the Evolution of Myelopathic Albumosuria," 'Brit. Med. Journ.,' July 13th, 1901, p. 75. Obituary notice on Dr. P. F. Colrat, 'Brit. Med. Journ.,' September 7th, 1901.)

The patient was a well-known French physician of Lyons, aged 55. The Bence-Jones proteid first appeared in the urine in December, 1899; the amount was at first very little, but it gradually increased and ultimately reached a maximum proportion of ten per mille. Death occurred from pneumonia in August, 1901. In this case Bradshaw ('Lancet,' October 4th, 1902, p. 931) says he observed a semi-fluctuating swelling of about the size of a large hen's egg in connection with one of the ribs.

No. 20. *The case of Iglehart, Hamburger, and Simon.*— (L. P. Hamburger, "Two Examples of Bence-Jones Albumosuria associated with Multiple Myeloma," 'Johns Hopkins Hospital Bulletin,' February, 1901, p. 38. C. E. Simon, "Observations on the Nature of the Bence-Jones Albumen," 'American Journ. Med. Sci.,' June, 1902, p. 939.)

The patient was a lady aged 49, whose first symptom was a sharp pain over one of the ribs in August, 1900. The examination of the urine led to the clinical diagnosis of multiple myeloma. Spontaneous fracture of the left femur occurred a few days before the patient's death in August, 1901. No necropsy was made.

No. 21. *The case of Osler, Hamburger, and MacCallum.*—(Hamburger, loc. cit. W. G. MacCallum, "A Case of Multiple Myeloma," 'Journ. Experimental Medicine,' 1901, vol. vi, p. 53.)

The patient was a coloured woman aged 50, admitted to the Johns Hopkins Hospital in October, 1900. The urine contained Bence-Jones proteid, and the clinical diagnosis of multiple myeloma was confirmed by the necropsy findings recorded by MacCallum.

No. 22. *Kalischer's case.*—(S. Kalischer, "Ein Fall von Ausscheidung des Bence-Jones'schen Eiweisskörper," 'Deut. med. Wochenschr.,' 1901, No. 4, p. 54.)

The patient was a woman aged 67. In this case a spontaneous precipitate (supposed to be of the Bence-Jones proteid) was observed in the urine on allowing it to stand for a long time. After death, examination of the ribs showed a tumour-like hyperplasia of the bone-marrow. Professor Loewy failed to detect the presence of Bence-Jones proteid in the bone-marrow from the ribs and humerus. It may be noted that one of the patient's daughters had died at the age of thirty of "pernicious anæmia."

No. 23. *Rostoski's case.*—(O. Rostoski, "Albumosurie und Peptonurie," at the meeting of the Phys.-med. Ges. zu Würzburg, June 13th, 1901, reported in the 'Sitzungs-Berichte,' 1901, Nos. 2 and 3; abstract in 'Muenchener med. Wochenschrift,' July 2nd, 1901.)

Rostoski gives no details of this case, but from the results of his examination of the urine, says that he inclines to the view of Magnus-Levy, that the Bence-Jones proteid (at least, what he found in his case) is not to be classed as an albumose. He has likewise recorded certain investigations regarding the Bence-Jones body in his paper "Zur Kenntniss der Präcipitine" (Würzburg, 1902).

No. 24. *The case of Jochmann and Schumm.*—(G. Joch-

mann and O. Schumm, "Typische Albumosurie bei echter Osteomalacie," 'Muenchener med. Wochenschrift,' August 20th, 1901, p. 1340; and "Zur Kenntniss des Myeloms und der Sogenannten Kahler'schen Krankheit," 'Zeitschrift für klin. Medicin,' 1902, vol. xlvi, p. 445.)

The patient was a woman aged 37, who was admitted to the Hamburg-Eppendorf Hospital in November, 1900. Her illness commenced with pains in the hips. Afterwards she suffered from pains in the loins and sternum, progressive kyphosis, spontaneous fractures of the thighbones, and increasing debility. She died from pneumonia, one and a half years after the commencement of the illness. During the last weeks of life her urine contained a considerable quantity of Bence-Jones proteid. She likewise had nephritis and hæmorrhagic glaucoma. After death an albumose-like body was detected in the blood. Though the authors originally considered that the case was one of genuine osteomalacia, their description of the post-mortem examination gave rise to considerable doubt as to the correctness of their view. Dr. T. R. Bradshaw, in a short communication on the subject ('Muenchener med. Woch.,' February 4th, 1902, p. 191), enumerated the main objections to the acceptance of their pathological inferences, and the authors afterwards republished the case as one of multiple myeloma. It should be noted that in this case the pelvis and long bones were affected, as well as the ribs and vertebral column.

No. 25. *Donetti's case.*—(E. Donetti, "Sulla Malattia di Kahler," 'Rivista Critica di Clinica Medica,' Florence, 1901, No. 46, p. 789.)

The patient was a man aged 45, with a painful affection of the bones, especially of the vertebral column and ribs, with anæmia, and with Bence-Jones proteid constantly in his urine. The method of D'Allocco seemed to demonstrate the presence of Bence-Jones proteid in the blood (compare Case No. 15).

No. 26. *The case of Hijmans van den Bergh, of Rotter-*

dam.—(A. Grutterink and C. J. de Graaff, "Ueber die Darstellung einer Krystallinischen Harnalbumose," Hoppe-Seyler's 'Zeitsch. für phys. Chemie,' 1902, vol. xxxiv, p. 393. A. A. Hijmans van den Bergh, "Albumosurie," reprinted from 'Herinnerungs-Bundel Prof. Rosenstein,' 1902.)

The patient, a manservant aged 36 years, had enjoyed good health till September, 1900, when he was seized with pain on the left side of the chest. Afterwards he had pains on the right side of the chest, in the right shoulder, and in the back. He had to give up work, and was admitted into the Rotterdam Hospital in March, 1901. In the hospital great deformity of the thorax occurred from progressive bending of the vertebral column and sternum, and death took place in December, 1901. At the necropsy the bone-marrow of vertebræ, sternum, and ribs was found transformed into a sarcoma-like growth. A femur was examined and found similarly affected, but in a lesser degree. The liver was fatty, and the kidneys showed slight interstitial changes. Miss Grutterink and Miss de Graaff succeeded in obtaining the Bence-Jones proteid in a crystalline form from the urine of this case. I have to thank Dr. Bradshaw for kindly placing a copy of Dr. Hijmans van den Bergh's paper at my disposal.

No. 27. *Conti's case.*—(Pietro Conti, "Albumosuria e Neoplasie Sistematiche delle Ossa," 'La Clinica Medica Italiana,' Milan, 1902, pp. 211—247.)

The patient was a lady aged 60, whose first symptoms were costal pains in August, 1899, when she was at the health resort of Mont-Dore on account of bronchial catarrh. She died October 30th, 1901, after about twenty-six months of suffering. The symptoms of the skeletal disease were chiefly referable to the bones of the trunk—pains connected with the ribs, sternum, and spinal column; kyphosis; and little tumours on the sternum and right ilium. There was cachexia, and

towards the end the muscular weakness was extreme. Bence-Jones proteid was first detected in the urine in November, 1900. For several weeks prior to the death of the patient, the urine is said to have contained albumen, but no longer any Bence-Jones proteid; it likewise contained hyaline and a few granular casts. Unfortunately no post-mortem examination was made. I am indebted to Dr. A. E. Garrod for drawing my attention to Conti's publication.

No. 28. *The present case.*—(Abstract already given.)

Uncertain Cases, and Cases in which the Reactions of the Proteid in the Urine were not quite Characteristic.

No. 29.—Dr. Sidney Martin (discussion on Dr. Bradshaw's paper, 'Proceedings of the Royal Med. and Chir. Soc.,' 1898, third series, vol. x, p. 120) referred to the case of a woman under the care of Dr. H. R. Spencer, at University College Hospital, for an ovarian tumour, which was removed. The urine, sometimes milky from precipitation of the proteid, was examined by Dr. Sidney Martin, who states that it contained "the same body or bodies" as those referred to by Dr. Bradshaw in his case. The subsequent history of the case is not given.

No. 30.—Dr. R. Hutchison (discussion on the "Proteids in Urine," 'Trans. Path. Soc.,' London, 1900, vol. li, p. 146) referred to a man who died in the London Hospital with multiple tumours of bones (extremities, ribs, and vertebræ). A flocculent precipitate separated out from the urine at 58° C., but did not re-dissolve on boiling. In this respect, and in its behaviour to nitric acid, the substance present in the urine had not quite the characteristic reactions of Bence-Jones proteid. The case should certainly, however, be mentioned here. Dr. Hutchison kindly informs me that the patient was 38 years old and

died within a week of admission. The upper end of one humerus, preserved in the London Hospital Museum, is much enlarged by a very vascular growth. Sections from one of the growths show it to consist chiefly of rather large rounded or polygonal cells with a good deal of protoplasm around a medium-sized nucleus. The protoplasm of many of the cells, Dr. Hutchison tells me, contained granules, possibly of the same nature as those in the tumour-cells of my case, J. T—.

No. 31.—Dr. Lee Dickinson (discussion on the "Proteids in Urine," 'Trans. Path. Soc.,' London, 1900, vol. li, p. 170) mentioned a case of leucocythæmia in the practice of Mr. Edgecombe Venning, in which Bence-Jones proteid—or, at all events, a proteid coagulating like Bence-Jones proteid at a relatively low temperature—occurred in the urine, and in which no other disease but leucocythæmia could be found.

Supposed Cases which have been incorrectly included in Summaries of Bence-Jones Albumosuria Cases.

No. 32.—A case described by Byrom-Bramwell and Noel-Paton ("On a Crystalline Globulin occurring in Human Urine," 'Reports from the Laboratory of the Royal College of Physicians,' Edinburgh, 1892, vol. iv, p. 47) was at one time regarded by Huppert ("Ueber einen Fall von Albumosurie," 'Hoppe-Seyler's Zeitschrift für phys. Chemie,' vol. xxiii, p. 500) as an instance. But after himself examining the proteid from the urine in question, he altered his mind ("Ueber den Noel-Paton'schen Eiweisskörper," 'Centralblatt f. d. med. Wiss.,' July 9th, 1898, p. 481) and regarded the substance as a globulin. The case is remarkable for the spontaneous precipitation of the proteid in crystalline form on allowing the urine to stand for a longer or shorter period, sometimes a day or two, sometimes weeks or months.

No. 33.—Simon ('Amer. Journ. Med. Sci.,' June, 1902, p. 954) wrongly cites a case reported by Karl Ewald ("Ein chirurgisch-interessanter Fall von Myelom," 'Wiener klin. Wochenschrift,' 1897, p. 169). The patient was a man aged 62. The diagnosis of myeloma was made during life owing to the examination of part of a growth removed from the right clavicle in April, 1894. Death occurred in May of the same year. No necropsy is recorded, and Bence-Jones proteid is not said to have been found in the urine. The case, therefore, cannot be accepted as an example of multiple myeloma with Bence-Jones albumosuria, although Jochmann and Schumm ('Zeitschr. f. klin. Med.,' 1902, vol. xlvi, p. 467), as well as Simon, have referred to it as such.

No. 34.—A supposed case of Dr. Vladimir de Holstein ('Semaine Médicale,' 1898, p. 206, and 1899, p. 83) is likewise referred to by Simon (loc. cit., p. 955), who states that the diagnosis of "multiple myelomatosis" was made during life owing to the state of the urine, and that the diagnosis was confirmed by a subsequent necropsy. However, on looking up Simon's references, I could only find a notice of Bradshaw's case, and a short *résumé* of the subject by Dr. V. de Holstein, but no new case.

In conclusion, I must express my thanks to those who have so kindly helped me in this account, only a small part of which I can fairly call my own. Besides Dr. R. Hutchison and Dr. J. J. R. Macleod, I have already mentioned a number of those to whom I am indebted for assistance: Professor R. Muir, of Glasgow, for his report on the tumour tissue and for other information; Dr. J. M. H. MacLeod and Dr. Gustav Mann, in regard to the examination of some of the tumour-cells; Dr. F. E. Batten, for examination of the nervous tissues; and Dr. J. H. Drysdale, for examination of the blood. Mr. S. G. Shattock has helped me very much in the pathological examination

of the skeleton and viscera, and Dr. A. E. Garrod in the examination of the urine. I must likewise thank Dr. Deugler, the house physician during the time that the patient was in the hospital, for the trouble he has taken in connection with the case; and my colleague, Dr. J. P. zum Busch, for kindly allowing me to use the photograph of the spinal arthropathy patient for comparison. To Dr. T. R. Bradshaw, of Liverpool, I am not only indebted for his published works on the subject; he took the trouble of coming to the German Hospital specially to examine the patient, and owing to his previous experience he was able to give valuable confirmation to the diagnosis. Through his kindness, moreover, I have previously become acquainted with some of the reactions of the Bence-Jones proteid in urine, for owing to some correspondence in regard to my previous case of multiple myeloma, he sent me in June, 1898, a bottle of characteristic urine from the patient he then had under observation (Case No. 10 in the Summary). I have also to thank Mr. Shiells for his care in the coloured drawing of the tumour.

APPENDIX.

Additional Cases of Bence-Jones Albumosuria.

Dr. J. M. Anders and Dr. L. N. Boston, of Philadelphia, have recently published[1] notes of three cases of Bence-Jones albumosuria.

Case A.—A well-developed man, aged 32, fond of athletics. He had had malaria at the age of twenty. In September, 1900, he had a severe fall, and afterwards complained of soreness in the dorsal and lumbar regions.

[1] "Bence-Jones Albumosuria," 'Lancet,' January 10th, 1903, p. 93.

In November of the same year he suffered from an attack of herpes zoster on the right side, and he noticed that he was thirsty; at this time he was voiding 2900 c.c. urine in the twenty-four hours. In 1901 he complained of repeated attacks of pain, and what he described as feelings of "giving way" in the bones. Tumours appeared over one of the ribs, on the right femur, and behind the right tonsil. There was frequent and copious epistaxis. Examination of the blood showed a certain degree of anæmia. Vision was impaired, and L. W. Fox found definite ophthalmoscopic changes present: hæmorrhages, and white spots in the retina, and choked disc. The patient died on April 22nd, 1901, but no necropsy was permitted. In this case albumen was present in the urine together with the Bence-Jones body. The total proteid measured 2 to 3 per mille by Esbach's method, and the daily amount of urine was about 2900 c.c. No tube casts were ever detected.

Case B.—A man aged 43 years, of temperate habits, with a family history of gout, rheumatism, and severe headaches. He was seen for the first time by Dr. Anders in November, 1901. One year ago he had suffered during three weeks from acute articular rheumatism.[1] Three years ago he fractured his right leg in a bicycle accident. In January, 1901, he was thought to have nephritis, and afterwards rapidly lost weight and strength, suffering likewise from pains in the extremities and back, and severe attacks resembling hemicrania. Examination of the blood showed deficiency in hæmoglobin and red cells. Retinal hæmorrhages were detected in both eyes. The patient died in 1902, but a necropsy could not be obtained. In this case the daily quantity of urine was 2500 c.c., but later on only 1875 c.c. The total proteid never exceeded 2·33 per mille by Esbach's method; during the last month of life, however, it was much reduced, and a reaction for

[1] In regard to the question of acute rheumatism, compare the post-mortem findings in the heart of my case J. T—.

the Bence-Jones body could no longer be obtained.[1] No tube casts were seen.

Case C.—A man aged 33 years, with a family history of gout, rheumatism, and Bright's disease. Six years ago, when he applied for life assurance, albumen and casts were detected in his urine. On examination in October, 1900, moderate enlargement of the left ventricle of the heart was made out. The retinal changes of chronic interstitial nephritis were found present in the right eye, but not in the left. There was some emaciation and anæmia. When the patient was last seen the disease seemed not to have made much progress. The urine (daily quantity, 2300 c.c.) was of specific gravity 1008—1012, and contained albumen. By Esbach's tube the total amount of proteid was estimated at only one tenth to three tenths per mille. The presence of the Bence-Jones body, as well as the albumen, was first ascertained in October, 1901, but it did not become a constant constituent till recently. Hyaline, granular, and the so-called amyloid casts were detected in the urine whenever searched for.

In their review of the subject, Dr. Anders and Dr. Boston speak of symptoms having been present in certain percentages of the cases, but it is not clear which cases these authors have admitted as genuine ones of Bence-Jones albumosuria. They allude to thirty cases which they have collected from the literature, but amongst them they seem to have included several in which there is no evidence that any albumosuria was present. The case of Professor R. von Jaksch, to which they refer, was shown at the Society of German Physicians in Prague on December 2nd, 1892. The patient was a woman with typical symptoms of Graves' disease, and with a swelling of the lower extremities which Jaksch thought might be of myxœdema-

[1] See Case No. 2 in my Summary of Cases.

tous nature; but no albumosuria was reported.[1] They quote K. Ewald's case of myeloma,[2] in the account of which there is no record of the Bence-Jones body, or of any albumose being detected in the urine. They have apparently likewise included H. F. Vickery's case[3] of "pseudo-leukæmia" in a patient aged 19 years, whose urine contained the "slightest possible trace of albumen," but nothing of the nature of the Bence-Jones body. Nor was any kind of albumosuria reported in either of the patients of J. H. Musser,[4] to whom they refer as having published a case. The case of Dreschfeld and Milroy, which they quote, had, however, escaped me.

Case D.—(J. A. Milroy, "A Contribution to our Knowledge of a Rare Form of Albumose occurring in the Urine," 'Journal of Pathology,' Edinburgh and London, 1901, vol. vii, p. 95.)

The man was an in-patient at the Manchester Infirmary twice during the year 1898, but his subsequent history is not known. Dr. Dreschfeld's notes point to there being new growths in the ribs and vertebræ. A hard painless growth was observed on one of the lower ribs on the right side. Milroy's paper discusses the nature and reactions of the Bence-Jones body in the urine.

Case E.—Sir Lauder Brunton kindly informs me that Dr. David Young, of Rome, had a case of Bence-Jones

[1] See report of the case in 'Prager medicinische Wochenschrift,' 1892, vol. xvii, p. 602.

[2] 'Wiener klinische Wochenschrift,' 1897, p. 169. See Case No. 33 of my Summary of Cases.

[3] "Pseudo-leukæmia with Chronic Relapsing Fever," 'International Clinics,' twelfth series, 1902, vol. ii, p. 89.

[4] "Note on the Fever of Hodgkin's Disease," 'American Medicine,' January 4th, 1903, p. 13. In this paper Musser describes two cases, one of which he regards as an example of Hodgkin's disease with tuberculosis, the other as "so-called Hodgkin's disease in which the clinical course was that of tuberculosis," and in which tubercle bacilli were present in the sputum. In neither of these cases was any albumosuria recorded.

albumosuria in which on precipitating the Bence-Jones proteid in the urine with alcohol the precipitate seemed to equal the height of one third of the whole mixture. There was probably no post-mortem examination in this case.

Case F.—(O. Langendorff and J. Mommsen, "Beiträge zur Kenntniss der Osteomalacie," 'Virchow's Archiv,' 1877, vol. lxix, pp. 452—487.)

I have to thank Professor Baeumler, of Freiburg, in Baden, for drawing my attention to this case, which was perhaps one of multiple myeloma with Bence-Jones albumosuria, though at the time regarded as one of osteomalacia only. The patient, a tailor aged 38 years, began to have "rheumatic pains" in 1869, and, about four years later, he frequently suffered from fractures of bones without any considerable violence to account for them. His thorax became deformed, and he died during an attack of dyspnœa, October, 1875, in the clinic of Professor Czerny, of Freiburg. The cysts found in the bones of this case might perhaps have been due to hæmorrhages in connection with myelomatous growth. The urine was thought to contain a small amount of Bence-Jones proteid.

Case G.—P. Vignard and L. Gallavardin ("Du Myélome Multiple des Os avec Albumosurie," 'Revue de Chirurgie,' Paris, 1903, No. 1, p. 91) record the case of a man aged 56 years, who was admitted September, 1899, to the Hôtel Dieu, of Lyons, suffering from severe thoracic pains and cachexia. He died in a comatose condition a few days after admission. The necropsy showed multiple myeloma of the bones of the thorax, but there is no proof that any Bence-Jones proteid had been present in the urine (nitric acid had only given a slight precipitate).

Case H.—Dubost ('Thèse de Paris,' quoted by Vignard and Gallavardin, loc. cit.) gives the case of a man aged 46 years, who died in a collapsed condition, December,

1896, soon after admission to a hospital in Lille. The necropsy showed multiple tumours of the ribs, sternum, and vertebræ, doubtless a form of multiple myeloma. During life the chief symptoms had been severe lumbar pains and rapid cachexia. The urine was stated to contain 3·5 per mille albumen, but no special tests for the Bence-Jones proteid were employed.

Case I.—C. E. Campbell-Horsfall ('Lancet,' 1903, vol. i, p. 1166) gives the case of a man in whom temporary Bence-Jones albumosuria was observed during several days after a severe gunshot injury to the leg, which necessitated immediate amputation. Recovery took place.

Case K.—L. N. Boston ('American Journ. Med. Sciences,' April, 1903, p. 658) gives the case of a lady aged 50 years, whose left breast was removed in 1898 for supposed carcinoma, and who has been losing flesh and strength. In January, 1902, she had a severe fall, and six weeks later Bence-Jones proteid was first detected in the urine; it was absent, however, at some recent examinations. The patient likewise suffers from certain pains and paræsthesiæ.

DESCRIPTION OF PLATES.

Multiple Myeloma (Myelomatosis) with Bence-Jones Proteid in the Urine (F. Parkes Weber, M.D., F.R.C.P.).

Plate I.—The patient J. T—, with multiple myeloma and Bence-Jones albumosuria, to illustrate the kyphosis (from a photograph taken in December, 1900).

Plate II.—A patient with the kyphosis of spondylitis deformans (Pierre Marie's "spondylose rhizomélique") for comparison with the patient J. T— and Dr. Bradshaw's patient.

Parkes Weber: Multiple Myeloma. Plate I.

The patient, J. T—, with multiple myeloma and Bence-Jones albumosuria, to illustrate the kyphosis (from a photograph taken in December, 1900).

Bale and Danielsson, Ltd.

Parkes Weber: Multiple Myeloma. Plate II.

A patient with the kyphosis of spondylitis deformans (Pierre Marie's "spondylose rhizomélique") for comparison with the patient J. T. and Dr. Bradshaw's patient.

Bale and Danielsson, Ltd.

Parkes Weber: Multiple Myeloma, Plate III.

Dr. Bradshaw's patient (Case No. 10 in the Summary), with multiple myeloma and Bence-Jones albumosuria, to illustrate the kyphosis.

Adlard & Son, Imp.

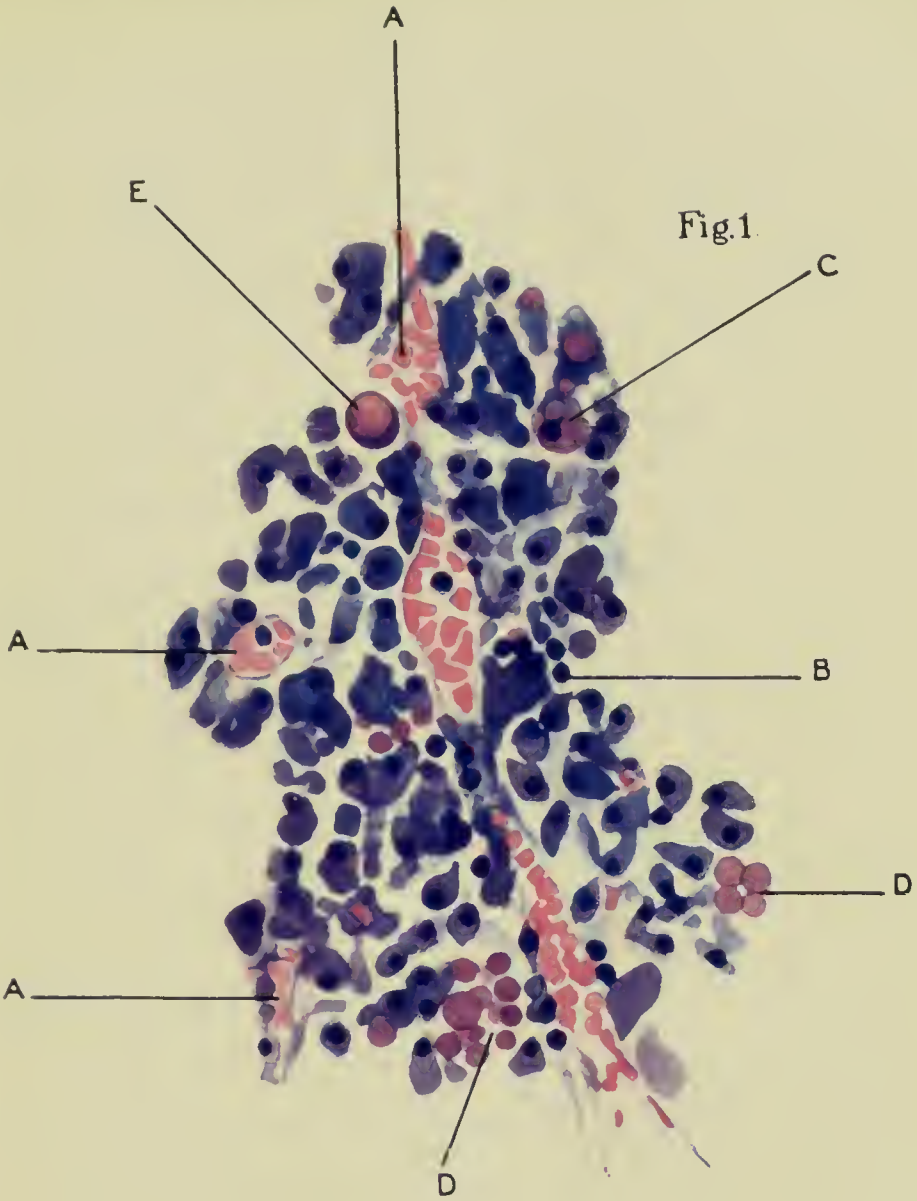

Fig.1.

Fig.3.

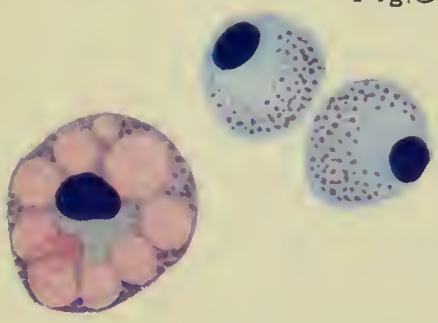

Fig.2.

Showing colour-reaction of the granules and globules of the tumour-cells. (*For description see end of paper.*)

PLATE III.—Dr. Bradshaw's patient (Case No. 10 in the Summary) with multiple myeloma and Bence-Jones albumosuria, to illustrate the kyphosis. Reproduced by permission from Dr. Bradshaw's paper in the 'Med.-Chir. Transactions,' vol. lxxxi.

PLATE IV.—To show colour reaction of the granules and globules of the tumour-cells.

FIG. 1.—Part of a section of the new growth (under oil immersion). A. Blood-vessel with thin walls filled with red blood-corpuscles. B. Cells resembling lymphocytes. C. Medium-sized globules in tumour-cell. D. Globules of various sizes free amongst the tumour-cells. E. Large globule, three or four times larger than a red blood-corpuscle, enclosed in a tumour-cell. The section was stained with hæmatoxylin after Mann's eosin and methyl-blue combination. The small granules in the tumour-cells are not seen. It will be observed that the globules, both those enclosed in tumour-cells and those lying free in the tissue, are stained differently to the red blood-corpuscles. In the big globule (E), however, the tint approaches more nearly that of the red corpuscles. The shape of the globules in question differs from that of the red blood-corpuscles in being almost perfectly spherical.

FIG. 2 (higher magnification).—A mulberry-like collection of globules, apparently formed in a single cell, of which the nucleus is visible.

FIG. 3.—Two tumour-cells showing granules and characteristic excentric position of the nucleus, which is surrounded by a zone free from granules; a larger tumour-cell containing granules and globules of various sizes. This figure is a semi-diagrammatic representation from a section sent me by Professor R. Muir, stained with Mann's eosin and methyl-blue combination without the additional hæmatoxylin which was employed in the preparations from which the first two figures were drawn.